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Editorial

The Congenital Bicuspid Aortic Valve

IT IS commonly taught that the congenital bicuspid aortic valve may function as perfectly as does the normal tricuspid aortic valve. One may wonder, however, about the wisdom of this teaching when certain facts concerning the congenital bicuspid aortic valve are reviewed.

The congenital bicuspid aortic valve in its pure state, without the addition of acquired disease, may be grossly incompetent as proved by clinical and necropsy observations. For example, a congenital bicuspid valve occurs in about 85 per cent of patients who have coaretation of the aorta; Christensen and Hines[1] observed basal diastolic murmurs in 20 per cent of a clinical series of 96 patients with coaretation of the aorta.

Bacterial endocarditis, which tends to involve tissue subjected to trauma, has a distinct predilection for the congenital bicuspid aortic valve. In almost half of the cases of aortic valvular bacterial endocarditis, the underlying disease is a congenital bicuspid aortic valve.

Smith and Matthews[2] re-emphasized the views of Peacock, expressed in the last century, that the congenital bicuspid valve is particularly prone to become calcified and therefore stenotic. It is recognized that a form of congenital aortic stenosis exists but, in this condition, the valve is essentially dome-shaped and not bicuspid. This anomaly is not the subject of this editorial, although the valve may acquire calcific change and in this way, perhaps, the degree of stenosis may become accentuated.

One must assume that the occurrence in a congenital bicuspid aortic valve of intrinsic insufficiency and the traumatic background leading to bacterial endocarditis results from improper closure of the valve. Furthermore, the tendency for congenital bicuspid aortic valves to calcify is perhaps also a manifestation of trauma related to improper closure. With this background suggesting that the congenital bicuspid aortic valve may close improperly, one may present some theoretic considerations on the relationship of function to the structure of the bicuspid aortic valve.

Consideration of the normal tricuspid aortic valve emphasizes how nearly perfect its structure is for its function. The three cusps of the normal aortic valve may be looked on as three independent units, each being connected to its respective segment of the aortic wall. Each cusp has two lateral attachments to the aortic wall and an inferior attachment to the root of the aorta. Between the two lateral attachments of a cusp the tissue is greater than the straight-line distance between the points of attachments. This extra length of tissue of a normal tricuspid aortic valve allows the central part of each cusp to extend to the center of the aortic orifice where it touches the other cusps during closure of the valve (fig. 1*a*). The excess

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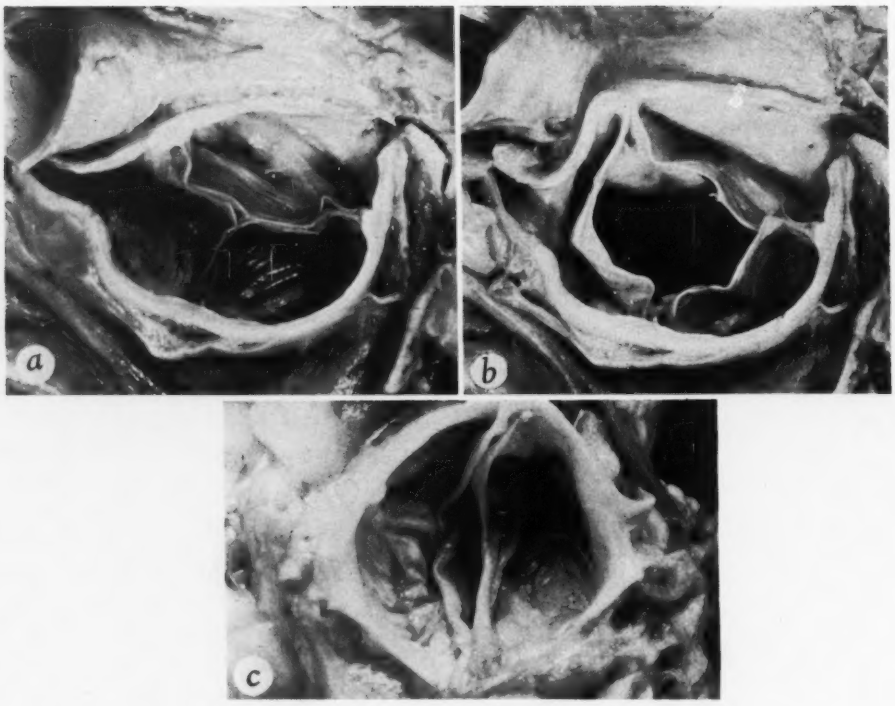

Figure 1

Normal tricuspid aortic valve in closed (a) *and opened* (b) *states.* (c) *Congenital bicuspid aortic valve.*

length also allows the individual cusps to balloon freely from the center of the orifice during systole, thereby allowing unobstructed opening of the valve (fig. 1*b*).

The anatomically perfect bicuspid aortic valve, if it actually ever exists, may now be considered. The length of the two cusps may be equal, or, as is more common, unequal. The length of each cusp is the same as the length of a straight line running between its two lateral attachments to the aortic wall. The individual cusp of the anatomically perfect congenital bicuspid aortic valve differs in this important way from the individual cusp of the normal tricuspid aortic valve. Because of this lack of extra length for free motion, the valve is held essentially fixed in a nearly closed state throughout the cardiac cycle (fig. 1*c*).

Thus, it becomes apparent that the anatomically perfect congenital bicuspid aortic valve would be stenotic because the individual cusps lack the extra length necessary for proper opening of the valve (fig. 2*a*). No evidence exists, however, that a congenital bicuspid aortic valve is intrinsically stenotic. One must therefore presume that two phenomena occur, singly or in combination, to prevent stenosis: (1) during ventricular systole, the aortic orifice becomes smaller, thereby creating a redundancy in the cusps that allows them to move freely away from the center of the orifice or (2) one or both of the cusps are longer than the straight-line length between their two lateral attachments. The extra length of the cusp would allow the mobility necessary for the valve to open during systole (fig. 2*b*, *c*, and *d*).

From the anatomic relationships of the aortic root to the myocardium, it is difficult

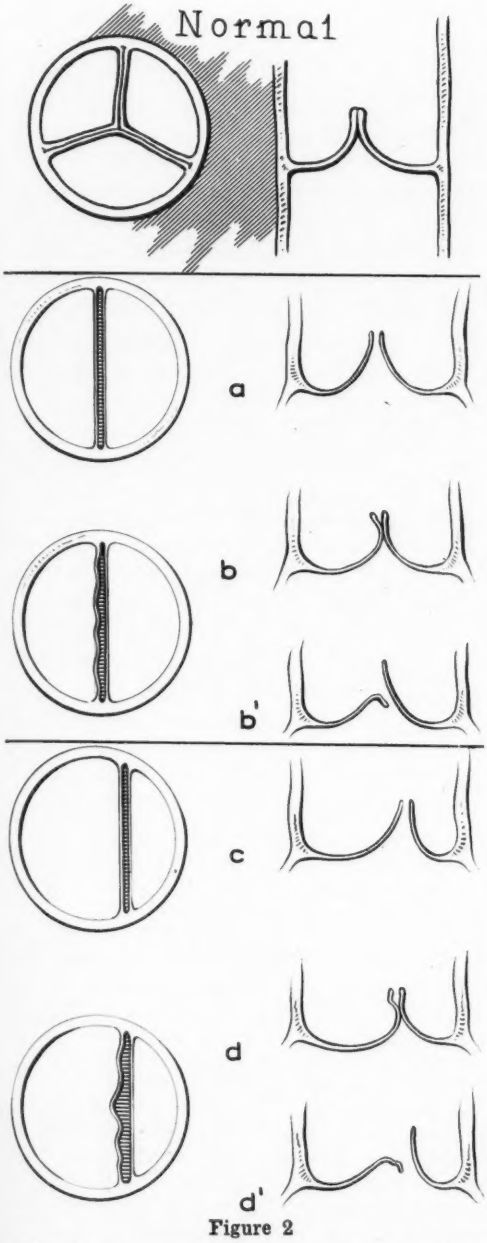

Figure 2

Diagrams of normal tricuspid aortic valve (top) *and congenital bicuspid aortic valve* (middle and bottom, a-d′). *In each instance the valve is viewed from above on the left and in a sagittal section on the right. In* a, b, *and* b′ (middle) *is portrayed a congenital bicuspid aortic valve in which the two leaflets are about the same length. In* a *is shown the hypothetically perfect bicuspid aortic valve in which the distance between the two lateral attachments of each cusp is equivalent to the straight-line distance between these two points. In* b *and* b′ *is portrayed the usual situation in which at least one of the two leaflets is longer than the hypothetically perfect cusp. This allows unobstructed opening of the valve. Closure of such a valve may be accomplished without incompetence* (b), *or with prolapse of the redundant cusp and resultant insufficiency (b′). A large regurgitant stream may push the opposite cusp away from the center of the aortic lumen during ventricular diastole and so accentuate the degree of aortic incompetence. In* c, d, *and* d′ (bottom) *is portrayed a congenital bicuspid aortic valve in which one leaflet is larger than the other. If there is no redundant tissue* (c), *the valve would be stenotic. If redundant tissue exists* (d *and* d′), *as is usually the case, the valve, while not stenotic, may be competent, or incompetent if prolapse occurs. The stresses resulting from redundant tissue with or without incompetence may be responsible for traumatic changes in the leaflet.*

to envision a mechanism that would cause the aortic orifice to narrow during ventricular systole. Therefore, absence of stenosis of the congenital bicuspid aortic valve is explained more readily by excessive length of one or both cusps. This is actually the usual finding.

While this anatomic fact is readily understood as a preventive of stenosis, it also explains the possibility of imperfect closure and of aortic valvular incompetence. During diastole, the free end of the cusp with excessive length may prolapse (fig. 2*b′* and *d′*). The regurgitant stream may strike the opposite cusp and traumatize it, causing it to be susceptible to bacterial endocarditis or to changes leading to calcification and stenosis. Moreover, the regurgitant stream, once established, may exert a greater force on the ventricular surface of the cusps than is the force on the sinus surface. In this way, the regurgitant stream perhaps may force open the aortic valve during diastole. If this does not happen, one cusp is pressed against its neighbor during diastole, the folding and unfolding of the long cusp may cause intrinsic trauma, and the pressure of the wrinkles of the elongated cusp on its opposite member may be

traumatic to the latter. Thus, the congenital bicuspid aortic valve, whether competent or incompetent, is potentially subjected to mechanical injury.

One begins to wonder about the validity of the theory that the anatomically perfect bicuspid aortic valve may be stenotic when one considers the state of the venous valves. The latter usually are bicuspid semilunar valves with considerable similarity in structure to the congenital bicuspid aortic valve. Yet the normal peripheral venous system offers no evidence of an obstructive factor. Perhaps this may be the result not of imperfections in the venous valves, as suggested for the congenital bicuspid aortic valve, but rather the result of dilatation of the vein at the site of a valve. Thus, while the venous valve may be so constructed as to be stenotic, the vein is larger at the site of the valve, and the diameter of the "stenotic" valvular orifice may be equal to that of the nondilated parts of the vein both above and below the valve.

The foregoing observations may be summarized as follows: the anatomic basis for the absence of intrinsic stenosis in the congenital bicuspid aortic valve is the very basis for the occurrence in this congenital anomaly of aortic valvular incompetence and also of traumatic influences that represent a tendency to the development of bacterial endocarditis and acquired calcific stenosis.

JESSE E. EDWARDS

References

1. CHRISTENSEN, N. A., AND HINES, E. A., JR.: Clinical features in coarctation of the aorta: A review of 96 cases. Proc. Staff Meet., Mayo Clin. 23: 339, 1948.
2. SMITH, D. E., AND MATTHEWS, M. B.: Aortic valvular stenosis with coarctation of the aorta: With special reference to the development of aortic stenosis upon congenital bicuspid valves. Brit. Heart J. 17: 198, 1955.

Laennec and his predecessors have assigned to diseases of the heart a certain series of symptoms, which they conceived to be common to the whole; but they had not analysed those symptoms and ascertained which were peculiar to, and pathognomonic of, the several affections taken individually. M. M. Bertin and Bouillaud, both writers of high talent, made this attempt, and with partial success; but the spirit of generalization, (if I am correct in my own view) carried them a grade too far. What observation leads me to regard as an inaccuracy constitutes the hinge of their work—the pivot on which turns the principal train of their reasoning: namely, that the symptoms of a retarded circulation are, under all circumstances, the result of *a mechanical obstacle* to the course of the blood —that when, for instance, they accompany hypertrophy or dilatation, they are not consequences of these affections, but of some co-existent mechanical obstacle, as a contracted valve, an aortic aneurism, etc. I have attempted to show, not only that hypertrophy and dilatation can, of themselves, respectively occasion the symptoms in question; but, that these symptoms are seldom produced in any very remarkable degree of severity by a mechanical obstacle, unless hypertrophy, dilatation, or softening of the heart is superadded.—J. HOPE, M.D. *Diseases of the Heart and Great Vessels.* London, William Kidd, 1832, p. 13.

Endocarditis Complicating Open-Heart Surgery

By JERE W. LORD, JR., M.D., ANTHONY M. IMPARATO, M.D., ALVIN HACKEL, M.D., AND EUGENIE F. DOYLE, M.D.

BACTERIAL ENDOCARDITIS following intracardiac surgery for congenital defects with use of extracorporeal circulation is a new entity, as old only as open intracardiac surgery. The reported experience is therefore meager. Suggestions regarding its pathogenesis, recognition, behavior, management, and prevention are few.

Heins and Linde[1] reported five cases of bacterial endocarditis in a series of 205 heart defects repaired with extracorporeal circulation. They stress the facts that the classical signs usually associated with bacterial endocarditis are absent and that the bacterial flora encountered is unusual and frequently antibiotic resistant. Two of their patients acquired their infection with achromobacter from a contaminated heart-lung machine when ethylene oxide sterilization rather than autoclaving was employed. One of their five cases died. Of additional interest, fever occurring shortly after surgery was the only clue that ultimately led to diagnosis.

Mandel et al.[2] first reported a case of bacterial endocarditis following repair of an interventricular septal defect. The operation was performed under hypothermia and coronary perfusion. The infecting organism was *Staphylococcus aureus*, and the patient died. Their review of the literature revealed 30 cases of endocarditis following operations for repair of congenital and acquired cardiac lesions but none of these was done with extracorporeal circulation.

Teitel and Florman[3] reported an unusual case of *Pseudomonas aeruginosa* infection on a silk suture used in the repair of an atrial septal defect with extracorporeal circulation. The infection resisted medical therapy until the infected suture was removed at a second operation 1 year later.

Two proved and one suspected case in a series of 20 operative procedures performed by our group for congenital cardiac defects performed with extracorporeal circulation prompted this report. It is thought that certain suggestions regarding its management might be deduced from the cases reported. Questionnaires sent to several groups performing this type of surgery are the basis for a summary of additional experience.

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Case Reports

Case 1

A. M., an 11-year-old girl was admitted to the hospital for surgical repair of an interventricular septal defect. On physical examination a grade-IV pansystolic murmur was audible over the entire precordium with maximal intensity in the pulmonic area. A grade-II middiastolic murmur was also heard at the left sternal border and at the apex. *Staphylococcus aureus hemolyticus*, coagulase positive, was found in culture of the nose and throat. This organism was sensitive to nine antibiotics including penicillin, chloramphenicol, and erythromycin.

On November 12, 1958, repair of the ventricular septal defect during extracorporeal circulation was undertaken. A Mark-Cooley oxygenator and Sigmamotor pumps were employed. An interventricular septal defect measuring 15 mm. in diameter was found high in the membranous septum and was repaired with a 10-mm. compressed Ivalon patch sutured in place with 3-0 braided silk continuous and interrupted sutures. The high location of the defect made suture of its upper margin difficult. Perfusion lasted 30 minutes, and the entire operation required 2 hours and 45 minutes. The patient withstood the procedure well and was returned to the recovery room in good condition.

Two and a half hours after surgery, the temperature had risen to 102.4 F., and through the sixth postoperative day the daily temperature peak was 102.8 or higher.

Procaine penicillin 400,000 units and streptomycin 0.5 Gm. intramuscularly twice daily had

been administered for 2 days prior to surgery and were continued the first 2 days postoperatively (fig. 1). Intravenous aqueous penicillin (1,000,000 units per day) was begun on the day of surgery. On the third postoperative day, the penicillin and streptomycin were discontinued because of urticaria and intravenous chloramphenicol (500 mg. twice daily) was begun. On the fifth postoperative day, this dosage was changed to 250 mg. intravenously every 6 hours.

Blood cultures drawn on the second, third, and fourth postoperative days grew *Staphylococcus aureus hemolyticus*, coagulase positive. In vitro sensitivity tests revealed the organism to be sensitive to chloramphenicol and novobiocin and resistant to penicillin. Subsequently on the fifth postoperative day, novobiocin (100 mg. every 6 hours intramuscularly), and aqueous penicillin (2,000,000 units per day intravenously) were instituted. Chloramphenicol was continued as chloramphenicol palmitate (250 mg. every 8 hours by mouth). On the sixth postoperative day, the daily dose of penicillin was increased to 20,000,000 units and probenecid (0.25 Gm. three times a day) was started. The patient improved clinically.

At this time, a new, prominent harsh systolic murmur was heard along the left sternal border. Reoperation was considered but was deferred in view of the patient's good clinical response to antibiotic therapy, and the mortality risk of a second surgical procedure. A careful examination of the literature yielded relatively little information useful in guiding us in the management of this problem.

The fever gradually subsided, six blood cultures drawn between the sixth and fifteen postoperative days were negative, and the previously mentioned murmur diminished in intensity. On the fifteenth postoperative day, penicillin, probenecid, and novobiocin were discontinued. Chloramphenicol was continued. On the nineteenth postoperative day, the temperature spiked to 101.6 F.; serial blood cultures drawn on the following 3 days grew *Staphylococcus aureus*, coagulase positive. The in vitro sensitivity tests were unchanged, and the temperature was not elevated at this time.

On the twenty-eighth day, because of the positive blood cultures, novobiocin and penicillin were restarted. The temperature dropped to within normal limits and the patient appeared to be doing well. Serial blood cultures were sterile.

On the forty-eighth postoperative day, 20 days after its readministration, penicillin was discontinued. The patient's clinical condition continued to be good, and on the sixty-sixth postoperative day, all antistaphylococcal medications were terminated.

Two days thereafter the temperature spiked to 104.8 F., the patient became toxic, and petechiae and splinter hemorrhages were noted. Serial blood cultures were positive for *Staphylococcus aureus*, coagulase positive. Despite vigorous antimicrobial therapy with a variety of anti-staphylococcal agents, the patient's clinical condition rapidly deteriorated. She died seventy-four days after surgery. Intracardiac postmortem blood cultures demonstrated *Staphylococcus aureus*.

Postmortem examination revealed the Ivalon sponge to be partially detached at the posterosuperior rim. A pulmonary thromboembolus was found in the left lower lobe.

Microscopic examination of sections of the Ivalon sponge and an overlying fibrinous deposit demonstrated dense infiltration of the fibrinous mass by hematoxylin-stained masses of cocci. A microscopic embolus containing clumps of cocci in a small arterial branch in the left lower lobe was also noted. No further site of infection could be found on the heart valves, in the region of the septal defect, or on the silk sutures.

Case 2

N. S. was a 12-year-old obese boy in whom the diagnosis of infundibular pulmonic stenosis with interventricular septal defect without clinical cyanosis was made on the basis of cardiac catheterization. Significant physical findings consisted of a grade-IV harsh systolic murmur heard best in the second left intercostal space. Nose culture yielded hemolytic staphylococcus albus, coagulase-positive, mannite negative, and sensitive to 10 antibiotics including penicillin, chloramphenicol, streptomycin, and erythromycin. (fig. 2). On September 24, 1959, through a transsternal incision with use of a Mark-Cooley oxygenator and Sigmamotor pumps for extracorporeal circulation and intermittent aortic occlusion to produce cardiac arrest, a 10-mm., high interventricular septal defect was repaired through a right ventriculotomy with interrupted 4-0 braided silk sutures. Closure was difficult, and closely placed sutures were necessary. The infundibular stenosis was corrected by removal of markedly fibrotic endocardium. The ventriculotomy was closed with continuous braided 3-0 silk. Total bypass time was 61 minutes, and the heart was open for 56 minutes. The only untoward reaction occurred early when transient superior vena caval obstruction of 10 to 15 minutes' duration was reported by the anesthesiologist.

The patient received no preoperative antibiotics, but postoperatively 300,000 units of procaine penicillin were given intramuscularly every 8 hours and 2 Gm. of chloramphenicol daily by continuous intravenous drip for 7 days. He awoke fairly promptly postoperatively but the next morning he became confused, developed car-

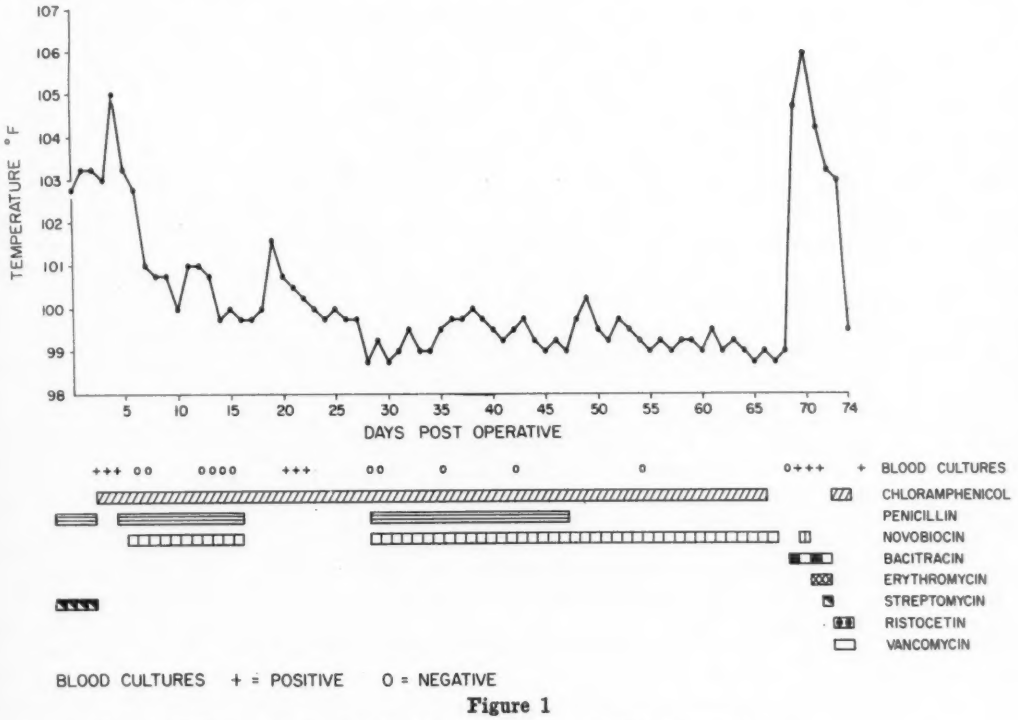

Figure 1

Case 1. Daily temperature peaks, blood cultures, and antibiotic agents.

pal spasm, and fever to 103 F. By the second postoperative day his temperature had reached 105 F., and carpopedal spasms with turning of the head to the right side and coma supervened. The white cell count was 18,000. A diagnosis of cerebral edema secondary to transient superior vena caval obstruction was made. A neurosurgeon advised acetazolamide (Diamox) 250 mg. intramuscularly daily, diphenylhydantoin sodium (Dilantin) 100 mg. intramuscularly every 4 hours, and phenobarbital in 0.060-Gm. doses as necessary to control convulsions. Cooling by use of a water mattress was also employed. The child's condition gradually improved with lightening of coma and subsidence of temperature to between 97.2 and 101 F. By the eighth day his sensorium cleared and blood cultures were negative, so that the chloramphenicol and the Diamox were discontinued.

On the ninth postoperative day he was digitalized because of a persistent tachycardia. Temperature again rose to 105 F., the white cell count was reported as 35,250, and erythromycin, 500 mg. every 6 hours, was administered. Blood cultures taken this day before starting erythromycin were sterile. During the next 48 hours fever to 102.6 F. persisted, and 10 million units daily of sodium and potassium penicillin were given by continuous intravenous drip. The murmur was of considerably diminished intensity. After another week, the general condition of the patient improved so markedly, and the temperature response had been so gratifying that, in the face of blood cultures which were repeatedly negative, intravenous penicillin was discontinued. Cultures taken during the next 2 days revealed hemolytic staphylococcus aureus resistant to all antibiotics except chloramphenicol, albamycin, kanamycin, vancomycin, and ristocetin. Since the sensitivity studies were not reported for some days, erythromycin was continued and 25 million units of penicillin were given daily by continuous intravenous drip as well as 500 mg. of probenecid every 6 hours. A week later because of continued fever, erythromycin was replaced with novobiocin, 500 mg. every 6 hours. Seventeen blood cultures and one bone marrow culture have since been negative. Penicillin and probenecid were discontinued after another week, and chloramphenicol, 2-Gm. daily, was resumed. Fever persisted and ranged between 98.6 F. and 103 F. although the peaks became progressively lower. At no time during his illness did this child show petechiae, hematuria, spleno-

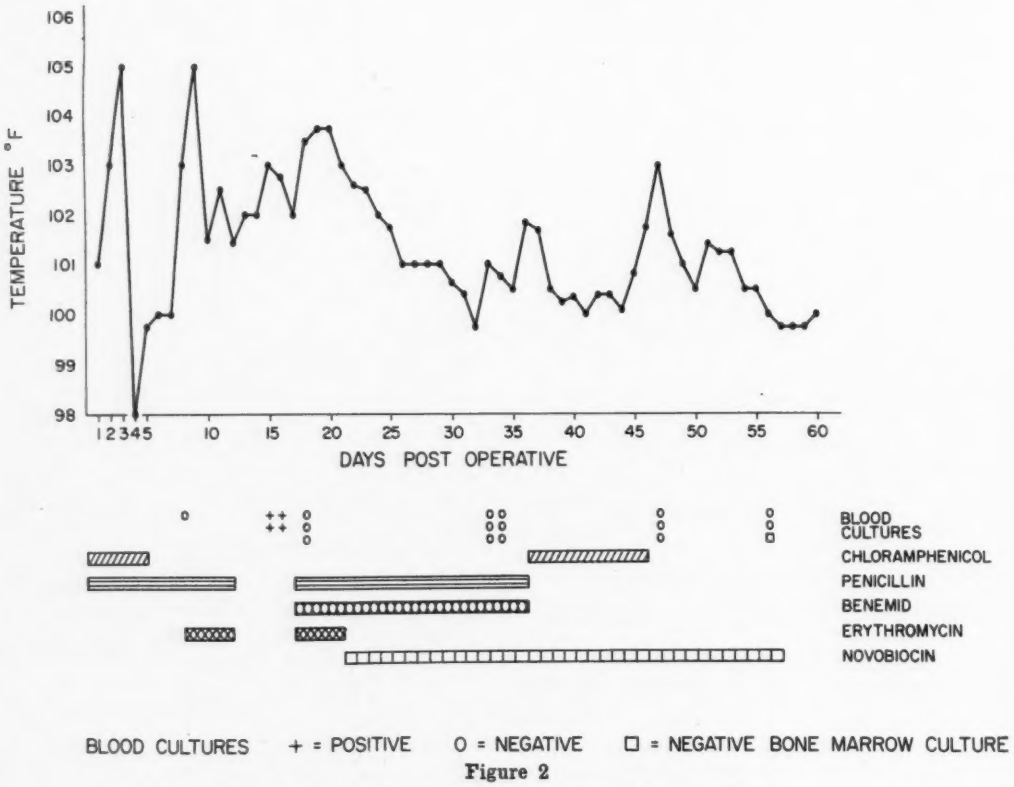

Figure 2

Case 2. Daily temperature peaks, blood cultures, and antibiotic agents.

megaly, or other evidence of embolic phenomena. Chloramphenicol was discontinued on November 9, 1959, and albamycin on November 23, 1959. Antibiotics were given for a total of 7 weeks.

At the present time except for a suture sinus at the lateral end of the transsternal incision the boy has made a complete recovery from his surgery and presumably from his infection.

Questionnaire Data

To learn the magnitude of the problem of infection in open-heart-surgery procedures for congenital cardiac defects, a questionnaire was sent to several groups throughout the country (table 1).

Discussion

The factors to be considered in evaluating the pathogenesis of surgical bacterial endocarditis may be classed into three main groups: bacterial factors, local host predisposing factors, systemic predisposing factors.

Bacterial Factors

Staphylococcus is the most commonly encountered organism in this disease and unfortunately also the most widespread pathogen in our environment. Pathogenic staphylococci, coagulase-positive strains, have been found[4] in from 25 to 30 per cent of cultures taken from normal adult noses and in 60 to 80 per cent of those from hospital personnel. In a series of 164 nose cultures taken from all personnel coming in contact with our cardiac surgical patients, 53 per cent grew Staphylococcus, 7 per cent of the pathogenic 80-81 phage type. One member of the team, responsible for the assembly of the heart-lung machine, was found to harbor this strain in his nose and might possibly have been the carrier in our first case. Skin and pharyngeal cultures of patients have also been found positive. Cultures of

Table 1

Occurrence of Bacterial Endocarditis Following Open Repair of Congenital Cardiac Defects with Extracorporeal Circulation

Total cases*	Mortality	Proved cases of endocarditis	Deaths from endocarditis	Incidence of staphylococcus endocarditis	Other organisms
2,585	19%	18	10	9	9†

Prostheses in infected cases	Groups using antibiotics prophylactically		Infection with preoperative antibiotics	Infections without preoperative antibiotics
	Preoperative	Postoperative	7 infections in 315 cases	11 infections in 2,170 cases
9	3	12		
	12% of cases	100% of cases	39% of infections in 12% of cases	61% of infections in 88% of cases

*Data from 12 groups reported by Dr. Henry T. Bahnson, Johns Hopkins Hospital, Baltimore, Md., Dr. George H. A. Clowes, Jr., Western Reserve University, Cleveland, Ohio, Dr. Denton A. Cooley, Baylor University, Houston, Texas, Dr. Frank Gerbode, Stanford University, San Francisco, Calif., Dr. Robert E. Gross, Children's Hospital, Boston, Mass., Dr. George Holswade, New York Hospital-Cornell Medical Center, New York, N. Y., Dr. George H. Humphreys II, Columbia Presbyterian Medical Center, New York, N. Y., Dr. Elliot S. Hurwitt and Dr. George E. Robinson, Montefiore Hospital, New York, N. Y., Dr. C. Walton Lillehei, University of Minnesota, Minneapolis, Minn., Dr. Leonard M. Linde, University of California at Los Angeles, Westwood, Calif., Dr. Jere Lord (authors' cases), and Dr. Andrew G. Morrow, National Heart Institute, Bethesda, Md. The authors gratefully acknowledge their assistance and cooperation.

†Other organisms were: 1, *Streptococcus fecalis;* 2, Achromobacter; 1, Pseudomonas; 2, *Candida guilliermondi;* 3, not specified.

operating room air almost invariably reveal organisms, sometimes as many as one colony per minute of exposure.[5] Air-borne staphylococci can be found in as many as 10 per cent of operative procedures.[6]

The mere presence of bacteria, however, is not sufficient to result in clinical infection. In a study of traumatic wounds, Rustigian and Cipriani[7] found that 100 per cent of the wounds contained large numbers of pathogenic bacteria covering a wide spectrum, while a relatively small percentage of patients developed clinical infection. An experimental evaluation of the factors that result in the development of clinical septicemia as opposed merely to bacteremia revealed that the virulence, kind, and dosage of organisms were extremely important.[8] Experimental animals tolerate intravenously administered bacteria to a certain number with complete clearing from the blood stream by the lungs and parenchymatous reticuloendothelial organs (liver, spleen, lymph nodes). Beyond that number clinical infection supervenes. The lethal dosage varies from a single anthrax bacillus to many billions of nonpathogenic bacteria. Dosage therefore is critical in the outcome of the introduction of any particular bacterial organism into the circulation.

Because of the ubiquity of the Staphylococcus no single measure can assure absolute sterility in the operating field.[6] Elaborate measures have been taken by some to control air-borne infection. These have included special masking devices in helmet form with an impermeable substance covering the nose and mouth and suction tubes to carry away exhalations. Careful attention to footwear and to traffic patterns, with introduction of decontamination zones prior to entry into the "sterile" operating area, are practicable measures.[9] Virtual elimination of conversation during surgery is indeed advisable. The use of ultraviolet light in the range of 2500 Å ± 200 (Ehrissmann and Noethling) to be used in the operating theater at all times is of proved value in greatly reducing the number of air-borne bacteria but has not found wide acceptance.[10, 11] Recently the incorporation of ultraviolet radiation into the air-conditioning system of the operating room has been reported to be of great benefit.[12]

The recent publications of Adams and Fahlman[9] have shown quite impressively that any area in an operating suite can be rendered nearly sterile by sufficient mechanical cleansing and by the application of detergent-disinfectant solutions to all articles entering or present within the suite. Proper isolation and protection technics then help to maintain this sterility.

Periodic culture studies of operating-room personnel and other contacts have revealed the presence of staphylococci at different times that have been difficult to eradicate permanently by either topical or systemic antibiotic therapy. Banning key personnel from the operating theater because of culture studies could have disastrous consequences on the performance of a medical unit. It would seem, therefore, that the other measures cited should be used to keep down the amount of air-borne contamination. In instances of personnel having infected skin lesions, however, it would seem imperative to ban these individuals from the operating theater.

Instrument and Pump Sterilization

Instrument and pump-borne contamination should be nonexistent with the availability of equipment that can be thoroughly cleaned of debris, autoclaved, and assembled under sterile conditions prior to use. In the data presented from other centers two infections were ascribed to pump contamination when ethylene oxide sterilization of the heart-lung machine was used. Kirklin is quoted by Teitel and Florman[3] as having experienced Pseudomonas infections during the time when the mechanical pump oxygenator was sterilized by filling with benzalkonium chloride (Zephiran). In January 1957, autoclave sterilization of all parts of the oxygenator except lucite reservoirs was introduced. The reservoirs were sterilized with formaldehyde, and infection was controlled. Keown[13] reported five cases of fatal Pseudomonas septicemia when their extracorporeal circulation apparatus was cold sterilized with Zephiran. When their mode of sterilization was changed, infection ceased to occur. All parts of the heart-lung machine coming in contact with blood are sterilized by autoclave in our hospital.

At two sites in the usual open-heart technic direct contact is made between sterile and nonsterile or nonautoclaved fomites—one at the coupling for pressure recordings, the other at the coupling of the oxygen tank to the oxygenator. Since Staphylococcus remains viable for weeks or even months when dried in pus or fomites, the possibility of massive contamination exists. Attempts have been made to pass the oxygen stream through various baffles but it would appear that infection would occur more often were this a portal of entry. Pressure gages are sterilized by immersion in Zephiran solution. Autoclaving would seem preferable but in view of the large numbers of right-sided heart catheterizations with pressure recordings that are performed daily without endocarditis, it would seem unlikely that this alone contributes significantly to contamination.

Dosage of Contaminating Organisms

It has long been recognized that repeated injections of small doses of organisms into the circulation are poorly tolerated. When septicemia was a more common problem than at present, it was known that septic thrombophlebitis was a relatively common cause of initiation and persistence of septicemia. Indeed we know of two cases, and a third is reported in the summary of reported cases, in which a septic thrombophlebitis, sometimes difficult to recognize as such, was responsible for septicemia and death of the patient. Accordingly, the formerly casual attitude towards venous cut-down has been changed so that it is now performed in the operating theater under the same conditions as the major portions of the operation. Polyethylene catheters are removed from veins as soon as possible. Although one of our patients repeatedly developed thrombophlebitis, septic thrombophlebitis could not be demonstrated. In one of the cases reported by Cooley (personal communication), septic thrombophlebitis was the focus for development of septicemia.

The unfortunate introduction of organisms via contaminated blood has frequently resulted in death because of the massive contamination involved. One of the cases reported by Cooley was thought to be due to contaminated blood but the patient survived. It is a credit to blood-banking activities that this accident does not occur more often, since the opportunity for contamination during skin puncture is ever present. Although normal serum will inhibit the growth of many bacteria, it will not inhibit the growth of pathogenic coagulase-producing bacteria.[14]

The possibility of infection being introduced by means of a plastic prosthesis in spite of the fact that it can be autoclaved is ever present. Autoclaving is subject to pitfalls, since adequate sterilization with steam requires contact with every portion of the surfaces to be sterilized. Failure to eliminate air pockets from prepared packs is known to result in incomplete sterilization because of failure of penetration of the steam. Cultures from the surfaces of a prosthesis would not reveal contamination within its interstices. Much the same can be said for braided or woven suture material and would perhaps suggest that monofilament suture material be used. In the reported cases a clear-cut correlation between the use of plastic intracardiac prostheses, Ivalon sponge, and infection cannot be drawn because of insufficient detail.

Local Predisposing Factors

Local factors that predispose to endocarditis following transient bacteremia have long been known. Damaged heart valves, arteriovenous shunts, and coaretation predispose to endocarditis. Rodbard[15] stated that vascular injury is not a prerequisite. High velocity flow through narrow orifices producing diminished lateral pressure locally determines the localization of the endocardial bacterial lesion. Endocarditis does not occur at large openings such as at interatrial septal defects or at the widely patent ductus arteriosus. If so, then absolutely complete closure of intracardiac defects with elimination of the very thin high-speed jets, which can occur between interrupted sutures or at needle holes, must be achieved to protect against bacterial endocarditis. It is difficult in the clinical case of infection at the site of closure of a defect to know whether the breakdown of a repair preceded or followed infection. In both of our cases there was difficulty in securing complete closure of the shunts, in the one because of the very high location of the interventricular septal defect with difficulty in finding adequate tissue to which to sew the upper border of the prosthesis, in the other because of persistence of a very small narrow jet between sutures.

The placing of foreign material within the heart, either a prosthesis or silk sutures, undoubtedly predisposes to infection. Elek and Coven[16] showed experimentally that the subcutaneous inoculum of pathogenic staphylococci required to produce local infection in human volunteers could be reduced by a factor of 10,000 by the introduction of a single silk suture into the area. Bahnson et al.[17] Jawetz,[18] and others have reported the persistence of infection around intravascular suture material. There seems little doubt that when infection persists or recurs in the presence of an intracardiac prosthesis, the prosthesis must be removed to eradicate the infection. In case 1, removal of the prosthesis immediately after infection recurred might have resulted in its elimination and possibly in survival of the patient. Whether the use of absorbable suture material is indicated is unsettled. It would appear at the present time that the use of nonabsorbable material is a necessary and unavoidable hazard in the repair of intracardiac defects.

Systemic Factors

Systemic factors of importance in the development of infection may exist but if they were important, infection should occur more frequently. Transient metabolic acidosis, transient thrombocytopenia, transient disorders of liver, adrenal, and kidney function occur so universally that it would be difficult to incriminate them in this process among the survivors. For those who die during the

early postoperative period, however, frequently with marked alteration of physiologic processes, conceivably defensive mechanisms could be so unalterably changed that an unrecognized failure to defend against infection also exists. In experimental animals[19] endocarditis can be produced on normal heart valves by the intravenous injection of staphylococci in the presence of arteriovenous fistulas. Presumably this occurs because of the increased work load imposed on the heart by the fistula. Dietary deficiency, shock injection of polysaccharides, bacterial extracts, cortisone, dinitrophenol, thyroxine, and organic acids, each is said to increase susceptibility to endocarditis.[20]

Therapy

Antibiotic therapy is of inestimable value in the treatment of the proved case of endocarditis. As prophylaxis, especially in the dosages usually employed, its value is debatable. Both of our patients received prophylactic antibiotics postoperatively; case 1 receiving it for 48 hours preoperatively as well. One developed infection with a chloramphenicol-sensitive strain after having received 2 Gm. of chloramphenicol intravenously for 6 days postoperatively. Does this signify endogenous infection, a newly acquired exogenous infection, or merely reexacerbation of previously existing but inadequately treated infection? Does this imply the emergence of antibiotic-resistant strains not recognized by our present bacteriologic methods? Does this indicate the need for more prolonged antibiotic therapy perhaps with a bactericidal rather than a bacteriostatic agent? In the absence of a large control series managed without prophylactic antibiotics, one can again only speculate. The study now being carried out by Kittle[21] in in which no prophylactic antibiotics are used in open-heart procedures should prove to be of great interest. Conceivably prophylactic antibiotics as now employed have helped to maintain the infection rate at its present overall low level.

The use of massive doses of penicillin as an adjunct in the treatment of "penicillin-resistant" staphylococcal infections is controversial. Resistant strains of this organism are found to produce penicillinase, which converts penicillin to penicilloic acid thus inactivating it. Penicillinase inhibitors (trypsin, chymotrypsin, quinine, and others) prevent this process. It is reasoned by some that perhaps penicillin itself in sufficient concentration will exhaust penicillinase activity. The crux of the controversy seems to hinge upon whether intrabacterial penicillinase can be so inhibited. Neither the need nor the ability of penicillin to accomplish this seems definitely settled. Clinical experience indicates that except when definitely penicillin-sensitive strains are encountered, even massive doses of penicillin used as the sole antibiotic cannot be relied upon to bring about clinical cure.[22]

The occurrence of 39 per cent of all the cases of endocarditis recorded here in the 12 per cent of patients in whom prophylactic preoperative antibiotics were used is striking. Whether unproved cases were cured by antibiotics or prevented by certain aspects of technic cannot be said at the present time. If the experience in the reported series is significant, it would appear that the preoperative prophylactic use of antibiotics is associated with a higher incidence of postoperative endocarditis. All groups here reported used prophylactic antibiotics postoperatively.

Recognition of Endocarditis

The detection and management of endocarditis poses special problems. Heins and Linde[1] stated that fever soon after surgery was often the sole clue. In our case 1 high fever 36 hours postoperatively associated with signs of pulmonary atelectasis was not suspected of being a sign of endocarditis, since this is a classical picture produced by these pulmonary changes during the early postoperative period. Blood cultures drawn 12 hours later revealed Staphylococcus. One wonders whether elimination of prophylactic antibiotics and repeated blood cultures during the first 3 days with antibiotic sensitivity

studies might not result in earlier diagnosis and more adequate and specific treatment with the very large doses of antibiotics required for eradication of this type of infection.

Conclusions

In conclusion, it would appear that the incidence of postoperative surgical endocarditis in patients who have had extracorporeal circulation for repair of congenital cardiac defects represents an unusual complication sustained not because of the casual low-grade contamination that occurs in every well-managed operating theater but rather because of massive contamination such as from contaminated blood, contaminated heart-lung machines, septic thrombophlebitis, or complete breakdown of aseptic technic. Early detection, as early as 24 to 48 hours postoperatively, depends entirely upon drawing frequent blood cultures, since it is during this period that fever, the major and frequently the only sign of postoperative endocarditis, occurs so often from relatively minor causes (atelectasis, blood in serous cavities, etc). Treatment for the proved case should probably be prolonged, specifically based upon studies of antibiotic bacterial sensitivity and probably include the use of bactericidal as well as bacteriostatic agents. Failure to respond to therapy or relapse after apparent response should lead to serious consideration of reoperation to remove infected foreign material from within the heart.

References

1. Heins, H. L., Jr., and Linde, L. M.: Bacterial endocarditis after surgery for congenital heart disease. New England J. Med. 263: 65, 1960.
2. Mandel, W., Hoffman, H. S., Heitzman, G. H., and Kass, I.: Endocarditis following ventricular septal defect repair. California Med. 88: 248, 1958.
3. Teitel, M., and Florman, A. L.: Postoperative endocarditis due to Pseudomonas aeruginosa. J.A.M.A. 172: 329, 1960.
4. Dubos, R. J.: Bacterial and Mycotic Infections in Man. Philadelphia, J. B. Lippincott Company, 1948.
5. Meleney, F. L.: The control of wound infections. Ann. Surg. 98: 151, 1953.
6. Wise, R. I., Sweeney, F. J., Jr., Haupt, G. J., and Waddell, M. A.: The environmental distribution of staphylococcus aureus in an operating suite. Ann. Surg. 149: 30, 1959.
7. Rustigian, R., and Cipriani, A.: The bacteriology of open wounds. J.A.M.A. 133: 224, 1947.
8. Hopkins, J. G., and Parker, J. T.: The effect of injections of hemolytic streptococci on susceptible and insusceptible animals. J. Exper. Med. 27: 1, 1918.
9. Adams, R., and Fahlman, B.: Sterility in operating rooms. Surg., Gynec. & Obst. 110: 367, 1960.
10. Meleny, F. L.: Treatise on Surgical Infections. London, Oxford University Press, 1948, p. 72.
11. Hart, D.: Bactericidal ultraviolet radiation in the operating room. J.A.M.A. 172: 1019, 1960.
12. New York Times, Sunday, February 21, 1960, p. 69.
13. Keown, K. K., Gilman, R. A., and Bailey, C. P.: Open heart Surgery. J.A.M.A. 165: 781, 1957.
14. Cohen, S.: Staphylococcal infections of the heart. Circulation 20: 96, 1959.
15. Rodbard, S.: Endocarditis and hydrodynamics. Abstract, Circulation 20: 758, 1960.
16. Elek, S. D., and Coven, P. E.: The virulence of Staphylococcus pyogenes for man. Brit J. Exper. Path. 38: 573, 1957.
17. Bahnson, H. T., Spencer, F. C., and Bennett, I. L., Jr.: Staphylococcal infection of the heart and great vessels due to silk sutures. Ann. Surg. 146: 399, 1957.
18. Jawetz, E.: The tough case of bacterial endocarditis. Circulation 20: 430, 1959.
19. Lillehei, C. W., Bobb, J. R. R., and Visscher, M. B.: Occurrences of endocarditis with valvular deformities in dogs with arteriovenous fistulas. Ann. Surg. 132: 577, 1950.
20. Highman, B., and Altland, P. D.: Effect of altitude and cobalt polycythemia, hypoxia and cortisone on susceptibility of rats to endocarditis. Circulation Research 3: 351, 1955.
21. Kittle, C. F.: Personal communication.
22. Antibiotics Annual 1958-1959: New York, Medical Encyclopedia, Inc., pp. 647-657; 1067-1068.

Primary Myocardial Disease

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DURING the past few years we have observed several patients who demonstrated cardiac enlargement and clinical symptoms and signs of congestive heart failure without convincing evidence of hypertension, coronary artery disease, or valvular heart disease. When death occurred, sometimes after years of chronic congestive heart failure, autopsy revealed none of the usual causes of heart disease. These patients were considered to have primary myocardial disease. In this paper is described a group of 17 such patients who have been subjected to postmortem examination at the Cincinnati General Hospital, the Cincinnati Veterans Hospital, or the Cincinnati Children's Hospital, and one patient from personal observation at the Brooklyn Hospital, Brooklyn, New York. Five of the patients were personally examined by one of the authors, and right-sided heart catheterization was performed in four of the patients.

Material and Methods

The diagnostic files of the Departments of Pathology of the Cincinnati General Hospital, Veterans Hospital, and Children's Hospital were searched for cases coded as myocardosis,* heart failure of unknown etiology, or as primary myocardial disease.† The files were examined for the last 30, 7, and 9 years respectively.

The patients who were included in this study were required to meet certain clinical and pathologic criteria. The specific clinical criteria for the selection of patients were (1) the presence of cardiac enlargement and congestive heart failure, except in two patients with nutritional cirrhosis; (2) the absence of sustained diastolic hypertension of 100 mm. Hg or more; (3) the absence of clinical or laboratory evidence of such renal disease as glomerulonephritis or chronic pyelonephritis or of collagen disease such as lupus erythematosus or scleroderma; (4) the absence of significant anemia, avitaminosis, thyrotoxicosis, or myxedema.

In all 18 patients autopsy protocols and microscopic sections were reviewed. In general the criterion for inclusion of patients in this group from the pathologic viewpoint was the finding of unexplained cardiomegaly. The specific pathologic criteria employed for excluding accepted causes of cardiac hypertrophy were (1) absence of significant coronary artery disease (three patients with a moderate degree of coronary arteriosclerosis were included in whom the arteriosclerotic process did not cause significant narrowing of the vessel lumen); (2) absence of other disorders commonly related to myocardial hypertrophy, such as intracardiac shunts or valvular disease; (3) absence of significant pulmonary parenchymal or vascular disease, such as severe pulmonary emphysema, severe pulmonary fibrosis, pulmonary sarcoidosis, or chronic recurrent pulmonary embolism; (4) absence of renal disease that could be related to clinically unidentified hypertension, such as glomerulonephritis, nephrosclerosis, or severe pyelonephritis; (5) absence of amyloidosis, collagen diseases, such as lupus erythematosus, dermatomyositis, or scleroderma, hemochromatosis, subendocardial fibroelastosis, or myocarditis.

The material used for pathologic study was routinely fixed in either Zenker's acetic acid, 5 per cent solution, or 10 per cent buffered formalin. One to eight sections of cardiac muscle were available for study in each patient (one in one case, two in four cases, three in three cases, four in six cases, six in three cases, and eight in one case). The routine stain employed was hematoxylin and eosin. Special stains were performed on appropriate material: (1) fat stains—Sudan IV (10 patients); (2) periodic acid Schiff digested and undigested—(all but no. 12 and no. 15); (3) crystal violet stain for amyloid (all but no. 12 and no. 14); (4) Van Gieson and trichrome stains (all but no. 12 and no. 14); (5) elastic tissue stains (all but no. 12 and no. 14). In addition the skeletal muscles were examined microscopically in seven instances.

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*Myocardosis: A term employed to describe significant enlargement of the heart unexplained by inflammatory, vascular, neoplastic, or neuromuscular disorders.[1]

†Primary myocardial disease is a subdivision of myocardosis but excludes beriberi, amyloidosis, hemochromatosis, and Von Gierke's disease.

Results

Clinical Observations

Eighteen patients were found to meet the clinical and pathologic criteria. These patients comprised the group referred to in this paper as primary myocardial disease. Fourteen of the patients were male, 11 were Caucasian, and seven were Negro. The youngest was 18 months and the oldest 68 years of age. Six were below the age of 40, six were from 40 to 49 years of age, and six were from 60 to 68 years of age. One of the female patients (no. 4, table 1) had several uneventful pregnancies. Congestive heart failure appeared for the first time several weeks after her last confinement.

A family history was available in only 13 of the entire group. Nine reported no family history of cardiac disease. Two (no. 9 and no. 13, table 1) gave a history of arteriosclerotic heart disease in close relatives, and one (no. 7) rheumatic fever in a younger member of the family. Only one (no. 12) reported similar heart disease in a brother.

No patient showed clinical evidence of pellagra, peripheral neuritis, or peripheral signs of high output failure. Three patients were reported to be heavy consumers of alcoholic beverages. Three other patients admitted a mild or moderate alcoholic intake.

In four patients (nos. 6, 8, 11, and 17) casual readings of blood pressure were elevated at some time during the period of observation. Patient 17 was treated for 2 years for congestive heart failure by a private physician. During this period of time a single record of 170 mm. Hg systolic pressure was reported. The blood pressure was always normal during the 7 subsequent years of observation. Patient 11 was observed for 15 years because of congestive heart failure and cardiomegaly beginning at the age of 31. After 2 years of observation, a casual blood pressure reading of 160/130 mm. Hg was reported. The blood pressure returned to normal after treatment for congestive heart failure and remained normal for the ensuing 13 years. Several months before he died he was seen during a bout of severe congestive heart failure. The blood pressure was elevated twice at 180/110 and 160/100. After treatment the pressure returned to normal levels a month later and remained normal until death. Patient 8 was first admitted because of subarachnoid bleeding. The blood pressure on the day of admission was 160/130 mm. Hg. The blood pressure returned to normal on the next day and remained normal throughout the subsequent year of observation for nutritional cirrhosis. His second and last admission 13 months later was because of congestive heart failure; his blood pressure was normal at this time. Patient 6 was also admitted because of subarachnoid bleeding and congestive heart failure. The blood pressure was elevated but subsequently returned to normal. He remained normotensive during a 2-year period of observation and treatment for congestive heart failure.

No patient gave a history of a febrile illness related to the onset of his disease. Sixteen subjects recalled the onset of their illness: shortness of breath, dyspnea, and dependent edema were the usual initial symptoms. Two of these patients were first seen with symptoms of frank pulmonary edema or paroxysmal nocturnal dyspnea. Six patients succumbed within 2 years after signs of congestive failure developed. In one the duration of congestive heart failure was not known, and in nine the duration was between 3 and 16 years. In two of the patients (nos. 9 and 14) with nutritional cirrhosis, the existence of heart disease was not suspected prior to necropsy. Ten of these 18 patients were hospitalized because of severe congestive heart failure on at least two occasions, and eight had been in the hospital only once. All but two patients had elevated venous pressure on each admission.

Twelve of the 18 patients had at some time systolic murmurs at the cardiac apex, aortic area, or left sternal border, graded two to four (grade-range one to six) in intensity. Extensive description of the murmurs was not given, nor was attention directed to their relation to respiration or to their duration.

Table 1

Pathologic Data in Eighteen Patients with Primary Myocardial Disease

Case no.	Heart wt.	Dilatation				Ventricular thickness (mm.)		Pericardium	Thrombi	Other diagnoses
		Rt. Atrium	Rt. Ventricle	Lt. Atrium	Lt. Ventricle	Rt. Ventricle	Lt. Ventricle			
E. B. 1	440*	+	+	+	+	7—10	2—16	normal	lt. vent.	pulm. infarcts
M. M. 2	468	—	—	—	—	3.5—5.0	10	normal	none	———
G. P. 3	565	+	+	+	+	4	20	900 ml. transudate	none	pulm. infarcts cardiac cirrhosis
V. H. 4	470	—	+	—	+	4	14	normal	lt. vent.	———
P. Y. 5	580	+	+	—	+	4	15	550 ml. transudate	rt. atrium lt. vent.	pulm. infarcts renal infarcts
C. F. 6	700	+	+	+	+	7	20	100 ml. transudate	none	———
N. B. 7	625	+	+	+	+	5	14	normal	rt. atrium, lt. vent.	fatty liver, mild
G. A. 8	575	—	—	—	—	4	20	normal	none	nutritional cirrhosis, early
P. G. 9	425	—	—	—	—	5-6	15	normal	none	nutritional cirrhosis, early
H. H. 10	675	+	+	+	+	not hypertrophied	?	normal	none	fatty liver
O. M. 11	655	+	+	+	+	3	5-10	normal	lt. vent.	renal infarction, recent
F. S. 12	440	—	—	—	—	5	18	———	both atria	splenic infarcts
W. M. 13	675	+	+	+	+	5	20	normal	rt. atrium	pulm. infarcts
G. V. 14	430	—	—	—	—	4	14	normal	none	nutritional cirrhosis
E. W. 15	500	+	+	+	+	4	14	normal	lt. atrium	pulm. infarcts
J. H. 16	625	+	+	+	+	6	20	normal	none	———
E. C. 17	625	+	+	+	+	10	17	normal	rt. atrium	———
H. K. 18	825	+	+	+	+	hypertrophied	hypertrophied	normal	atrial	pulm. infarcts

*Heart and lungs weighed together.

In three patients a diastolic rumbling murmur was heard in the mitral area; in two an early diastolic blowing murmur was localized at the left sternal border, during one of multiple admissions; these diastolic murmurs were not persistent. In four patients no murmurs were described: in eight a diastolic apical gallop rhythm was heard. As a rule, the gallop rhythm disappeared after intensive treatment for heart failure, to return during the next admission or shortly before the final illness. A significant paradoxical pulse was described once in one patient. Examinations of the ocular fundi were reported in 14 patients; 11 were described as normal. Two showed grade one and one showed grade two hypertensive changes, but none had hemorrhages or exudates. None of the patients had clinical evidence of thyrotoxicosis; none had a hemoglobin below 10 Gm. per 100 ml. of blood.

Serum protein values were available in

six patients; in only two was the albumin-globulin ratio reversed. The total protein values ranged from 5.3 to 7.2 Gm. per 100 ml. of blood, and the serum albumin values were between 1.3 to 3.65 Gm. per 100 ml.; only one patient had a serum albumin value below 2.5 Gm. per 100 ml. of blood.

Of the 18 patients, 16 had at least one electrocardiogram recorded and many had several during each admission. The electrocardiograms of three patients showed abnormal left axis deviation (mean QRS vector directed leftward beyond −30°) and each of the three had electrocardiographic evidence of left ventricular hypertrophy. Three others had a mean QRS vector greater than 110°, indicating abnormal right axis deviation; only one of these showed suggestive evidence of right ventricular hypertrophy. Biventricular hypertrophy was suspected in one patient without abnormal axis deviation. Two patients showed a mean QRS axis of −90°. Minor T-wave abnormalities were found in eight patients at some time during their illness. Only three patients of the entire group had definite low voltage of the QRS in the limb leads, but the QRS voltage was normal in the precordial leads. The low voltage QRS complexes in the limb leads were seen during severe congestive heart failure and disappeared with clinical improvement. Seven patients displayed chronic atrial fibrillation throughout the course of illness. Two others showed temporary first degree atrioventricular block, thought to be due to digitalis. In two patients ectopic atrial and nodal tachycardia and interference dissociation were observed while they were receiving digitalis.

Fifteen patients were examined radiologically on more than one occasion and in eight of these, cardiac fluoroscopy was performed; one had only a single radiologic examination. In no instance was there seen valvular or pericardial calcification, abnormal pulsations of the pulmonary artery, abnormally increased or decreased pulmonary vascularity, or paradoxical pulsation of the left ventricle. Four showed generalized diminution of cardiac pulsation. Pulmonary changes produced by congestion were common. Generalized enlargement of the cardiac silhouette was seen in all 15 patients. The left atrium was thought to be prominent in five patients. It was not otherwise possible to detect selective or predominant chamber enlargement. Kerley lines were found in only one patient (no. 3).

Right heart catheterization was performed in four patients. The data obtained were essentially the same in each of the four patients (table 2). The cardiac index was well below normal in the three subjects in whom it was calculated. The arteriovenous oxygen differences were considerably above normal values in all four subjects. The mean right atrial pressure and the right ventricular diastolic pressure were elevated in three patients; in the fourth patient right atrial pressure and right ventricular diastolic pressures were normal, suggesting right ventricular compensation at the time. The pulmonary arterial and wedge pressures were increased in the three patients in whom they were measured, suggesting left ventricular decompensation. The right ventricular pressure curve of patient 12 showed a high diastolic plateau but not a marked diastolic dip. The hemodynamic data were consistent with congestive heart failure involving both ventricles with a low cardiac output.

Venous angiocardiography was performed in patient 1 in order to exclude pericardial effusion. An extremely dilated right ventricle and prolonged circulation time were noted. No shunts or other abnormalities were visualized. The left atrium and ventricle were not opacified.

Systemic arterial embolism was not recognized clinically in any of these patients. The patients were treated with the usual regimen for cardiac failure by restriction of activity, low-sodium intake, digitalis, and diuretics. Antibiotic agents were used in most of the patients; one patient received cortisone for several months with no beneficial effect. Sixteen patients died with intractable heart failure; one (no. 14) died with septicemia, and one (no. 9) in coma as a result of aspiration pneumonia; in three instances pulmonary em-

Table 2

Right Heart Catheterization Data in Four Patients with Primary Myocardial Disease

Case no.	RA mm. Hg	RV mm. Hg	PA mm. Hg	PW mm. Hg	PAR dynes sec. cm.$^{-5}$	Systemic arterial oxygen saturation (per cent)	O_2 consumption ml./min.	CI L./min./M^2	CO L./min.	A-V O_2 difference ml./100 ml.	BP mm. Hg
1	mean 9	43/5-16	—	—	—	90.3	assumed 77	1.6	0.8	9.7	88/58 mean 65
3	17.8 mean 11.5	50/5-10	50/29 mean 36	27	375	97.8	147	1.1	1.9	7.9	—
11	mean 1.8	end-diastolic 3.0	50/24 mean 34	17	557	94.8	200	1.5	2.4	8.3	—
12	18	48/18	56/30	28	—	97.0		—	—	6.8	—

RA, right atrial pressure; RV, right ventricular pressure; PA, pulmonary arterial pressure; PW, pulmonary wedge pressure; PAR, pulmonary arteriolar resistance—dynes sec. cm.$^{-5}$; CI, cardiac index—liters per minute per square meter body surface; CO, cardiac output—liters per minute; AV, arteriovenous; BP, systemic blood pressure.

boli culminated the disease. The correct diagnosis was suspected clinically in only three patients. The cause of heart failure was listed as unknown in four; myocarditis was suspected in four, and in the remaining patients of the group rheumatic heart disease, arteriosclerotic heart disease or "collagen disease" was suspected to be the cause of the congestive heart failure.

Pathologic Observations

In 15 of the 18 patients coronary arteriosclerosis was slight or absent altogether. In the remaining three patients coronary artery disease was of moderate degree but was considered to be insufficient to account for the striking cardiac hypertrophy seen.

Cardiac hypertrophy was present in each instance. Exclusive of the 1½-year-old girl the hearts varied in weight from 425 to 825 Gm. (table 1). Usually the right and left ventricles were proportionately enlarged. The cardiac chambers were generally symmetric and in 13 cases dilated. In the remaining five cases the state of dilatation was not commented upon by the prosectors.

Intracardiac thrombi were encountered in 10 of the 18 patients in the left ventricle and in the atria (table 1). Embolism was noted in eight patients. Pulmonary infarction had occurred in six instances; in three there was no evidence of thrombus formation on the right side of the heart. Systemic embolic infarction was recognized in three subjects: the kidney was involved in two and the spleen in one.

Changes in the endocardium were inconspicuous and endocardial sclerosis was minimal. The epicardium was also normal.

The myocardial consistency was not the same in all instances. In four cases it was described as flabby, while in three the myocardium was said to be firm. There was no apparent correlation between the consistency and the postmortem interval or the extent of myocardial fibrosis.

While some degree of myocardial fibrosis was a frequent finding, it was usually absent (fig. 1, patient 6) or of slight degree, and in only four cases was it considered to be moderate (fig. 2, patient 3). There was no apparent correlation with mural or intramyocardial thrombosis, cardiac size, duration of heart failure, or the number of such periods of failure. In only one of the four instances of moderate fibrosis was the coronary arteriosclerosis more than slight and in this case (no. 12) a moderate degree of scarring was noted.

Except for an occasional small cluster of lymphocytes microscopic evidence of inflammation was not encountered. This reaction was thought to be inconsequential and not

indicative of significant acute or chronic myocarditis.

The individual muscle fibers were generally enlarged and there were only nonspecific associated alterations, seen as interstitial edema and vacuolization.[2] The pericardium in two patients (nos. 3 and 5, table 1) contained a large quantity of clear fluid (900 and 550 ml. respectively) and in one additional patient there was a mild transudate.

In a single case (no. 3) there were large quantities of deposit that was PAS-positive and diastase-resistant within myocardial fibers —especially with a perinuclear location (fig. 3). In three others an occasional focus of a similar material was found. Special stains were otherwise noncontributory. Amyloid stains were negative in 16 cases and the connective-tissue technics served only to confirm the presence of the fibrosis recognized in conventionally stained sections. Occasionally elastosis was manifest (fig. 4) over the convex portions of papillary muscles. In only one patient (no. 11) was fatty degeneration evident. This appeared as vacuolization of the sarcoplasm in occasional fibers and stained with Sudan IV.

Examination of the skeletal muscles revealed no significant lesions. In one instance (no. 3) cardiac cirrhosis was striking. In one patient (no. 14) there was advanced nutritional cirrhosis, and in two others early nutritional cirrhosis was observed. In one patient a mild degree of fatty infiltration of the liver was seen and in another a marked degree of fatty change was noted.

Discussion

When seen during life, the patient with primary myocardial disease is often considered to have hypertensive cardiovascular disease, rheumatic heart disease, coronary artery disease, or pericardial disease.

Some of these patients may have transient diastolic hypertension, presumably because patients who develop congestive heart failure may have an associated increased systemic vascular resistance.[3-7] In this study we have considered that the absence of sustained diastolic hypertension militates against a diagnosis of hypertensive cardiovascular disease. None of the patients in this study had grade three or four eye-ground changes, and none of them had nephrosclerosis, glomerulonephritis, or severe pyelonephritis at necropsy.

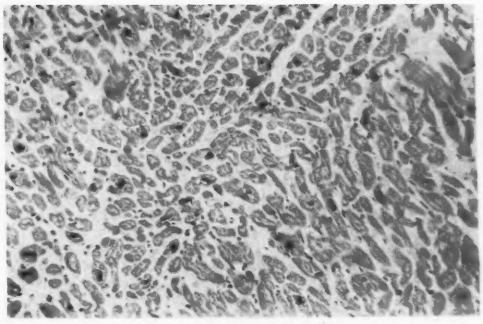

Figure 1

Microscopic section of the myocardium from case 6. No significant degree of fibrosis can be seen. Hematoxylin and eosin stain.

Both clinical and radiographic observations may suggest the presence of rheumatic heart disease. Many of these patients have cardiac murmurs, presumably resulting from cardiac dilatation during congestive heart failure. They may have systolic apical murmurs resulting from relative mitral incompetence or systolic murmurs closer to the left sternal border resulting from tricuspid incompetence. Occasionally diastolic gallop rhythms may be mistaken for a mid-diastolic murmur of mitral stenosis. The radiologic examination may also be misleading because disproportionate left atrial enlargement may be found. Another roentgen finding that may suggest rheumatic heart disease is the finding of Kerley lines. Usually, however, the decrease in the intensity of the murmurs with a response to treatment will cast a doubt on the diagnosis of rheumatic heart disease. This was well illustrated in one of our patients (no. 3, table 1), who had been considered for years to have rheumatic mitral valvular disease; however, the inconstant nature of his apical systolic murmur indicated that this was rather the result of cardiac dilatation.

Coronary artery disease is also difficult to

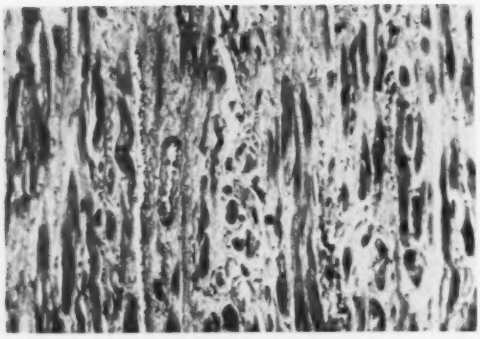

Figure 2

Microscopic section of the myocardium from case 3. Fibrosis with replacement of large portion of the myocardium is striking. This section represents the most severe grade of fibrosis seen. Hematoxylin and eosin stain.

exclude clinically. None of the patients in our group had angina pectoris; however, some patients may have electrocardiograms suggestive of previous infarction in association with abnormal left axis deviation or with left bundle-branch block. Frequently coronary artery disease is diagnosed clinically in this group as a diagnosis of exclusion because of its greater incidence than that of primary myocardial disease.

In addition many patients in this group were suspected at one time of having pericardial disease. The extreme cardiac dilatation seen in many of these patients often suggests the possibility of pericardial effusion. Furthermore, the feeble pulsations of the dilated heart may suggest to the radiologist pericardial effusion; however, the response of the venous pressure, edema, and hepatomegaly to the treatment for heart failure usually eliminates the diagnosis of pericardial disease. Paradoxical systemic arterial pulse may also be seen in primary myocardial disorders and again raises the question of pericardial involvement. Because patients with primary myocardial disease may have very high right ventricular diastolic pressure, right heart catheterization studies may be of little help in the differential diagnosis of these two disorders. In one of our patients (no. 12, table 2) right ventricular diastolic pressure exceeded one third of the systolic pressure, raising the question of cardiac constriction. Angiocardiography may be of value in excluding pericardial effusion or increased pericardial thickness.

The clinical picture of chronic myocarditis may resemble that of idiopathic myocardial disease. Kline and Saphir[8] described six patients with heart failure due to chronic myocarditis. The duration of heart failure in this group was relatively short, being from 5 weeks to 16 months in five instances but 4 years in the sixth patient. In each subject described by Kline and Saphir necropsy revealed some degree of myocardial inflammation that was largely interstitial and consisted principally of lymphocytes and histiocytes. This degree of inflammation was not seen in our patients. Other disorders that may affect the myocardium, such as hemochromatosis, gargoylism, and Marfan's syndrome, can usually be readily excluded by clinical examination. Von Gierke's disease and subendocardial fibroelastosis[9] are more difficult to differentiate from the disorder under question, and the distinction may be impossible during childhood. At necropsy the deposition of glycogen in the heart muscle fibers in Von Gierke's disease and the endocardial sclerosis and fibroelastosis make these diseases easily separable from primary myocardial disease. In the 7-year period studied at the Cincinnati Veterans Hospital, when eight instances of primary myocardial disease were found, no instance of subendocardial fibroelastosis was discovered.

Within the last 15 years several papers dealing with primary myocardial disease have been published. Spodick and Littman[10] reviewed the literature up to 1958 and gathered 72 reported cases, adding eight of their own. The disease occurred in relatively young adults with a rapid deteriorating course. Thirty per cent of the patients in this group were Negroes. Elster's[11] group of 10 patients was also largely composed of young adults. Only one patient was older than 50, whereas in our series six patients of the 18 were beyond this age. In Elster's group six of 10 were Negroes; three of the 10 patients were female. Elster[11] and Spodick[10] stressed the

relatively short course of the disease. Physical findings were similar in both reports and the most consistent clinical features were cardiac enlargement and evidence of congestive heart failure. Elster and Spodick also emphasized strongly the frequent occurrence of intracardiac thrombi and embolic phenomena. Elster[11] reported slightly elevated diastolic blood pressure in five of his 10 patients and related this elevation to heart failure. Spodick's[10] patients were normotensive. Our group of 18 patients differs in three respects: (1) there were more older patients in our group; (2) many patients in our group had congestive heart failure of long duration; and (3) there was a relatively low incidence of clinical systemic arterial embolism.

In the literature we could find only one description of right heart catheterization in a patient with idiopathic myocardial hypertrophy. This was reported in a discussion of Elster's paper[12] by Dickinson Richards. The data showed low cardiac output and slightly elevated pressures in the pulmonary artery as have been frequently found in individuals recovering from congestive heart failure.[13] Balchum, McCord, and Blount[14] reported right heart catheterization in two patients believed to have chronic myocarditis. The cardiac outputs were low, with increased arteriovenous oxygen difference. In a recent survey Lynfield and associates[15] reported hemodynamic findings in six children with idiopathic cardiomegaly and significant fibroelastosis. The hemodynamic data in our patients did not differ significantly from those described by Blount and Richards and were similar to those in a group of patients with chronic left ventricular failure recently reported by Selzer.[13]

In general the pertinent gross pathologic features of primary myocardial disease are those of a marked, usually symmetric hypertrophy, dilatation of all cardiac chambers and the frequent finding of intracardiac thrombi. The consistency of the myocardium may or may not be flabby. The cardiac muscle at times appears paler than normal. Grossly obvious fibrosis may or may not be present: when present, it tends to be most severe in the left ventricle. Significant endocardial sclerosis is infrequent.

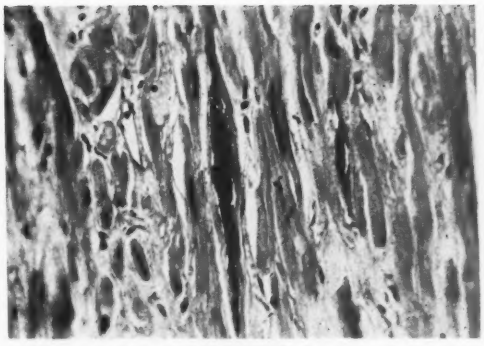

Figure 3

Microscopic section of the myocardium from case 3. The perinuclear deposit of PAS-positive, diastase-resistant material is prominent. Such deposits have no apparent relation to the degree of fibrosis.

The heart weights in our patients (average 579 Gm.) were comparable to those found by Elster and associates.[11] These authors recorded heart weights of 430 to 800 Gm. in 10 patients with cardiac hypertrophy of unknown etiology, the average weight being 575 Gm. In Levy and Von Glahn's study[16] heart weights were between 440 and 740 Gm. in 10 patients with idiopathic cardiac hypertrophy. Intracardiac mural thrombosis was noted in 10 of our 18 patients: the thrombi were in the ventricles, in the atria, and in atria and ventricles. The significance of such thrombosis is unknown. Elster and associates[11] also reported a high incidence of mural thrombosis of seven out of 10 instances. As in our series, Elster and associates found no severe myocardial fibrosis in their patients; in their group the fibrosis was principally subendocardial and endocardial. On the other hand, Levy and Von Glahn[16] found more extensive areas of necrosis and fibrosis in their patients but were unable to demonstrate any relationship of these lesions to those of mural thrombosis.

The mechanism of production of myocardial fibrosis in this disorder remains unknown. Some authorities believe that subendocardial elastosis, seen to a minor degree in some of our cases, is secondary to cardiac dilatation.[17-19] It is probable that the degree of

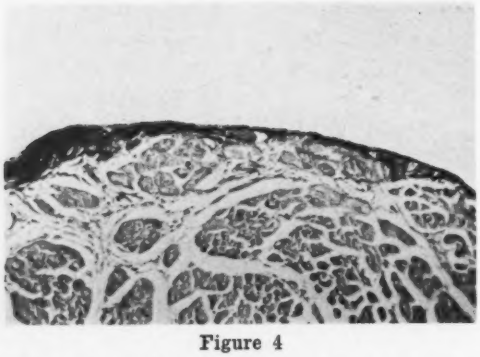

Figure 4

Microscopic section of the myocardium and endocardium from case 14. The small quantity of elastic tissue formed in the endocardium is observed. Elastic tissue stain.

dilatation in our patients was insufficient to produce more than the minor changes that were observed.

The significance of the PAS-positive material noted in one of our patients is uncertain. It is believed to be the same as the so-called basophilic degeneration.[20] This is a relatively common phenomenon in older individuals but its abundance in a young person is unusual (fig. 3).

Pathologic changes in the liver not secondary to heart failure were found in five subjects. Two subjects had fatty livers and three had nutritional cirrhosis. The incidence of alcoholism was high in the group from which these patients were obtained, and these changes in the liver may be coincidental rather than etiologic for the heart disease.

The etiology of primary myocardial disease is uncertain. It is quite possible that the patients included in our study represent several different disorders. Hereditary, infectious, and nutritional factors deserve consideration as possible etiologic mechanisms. It has been reported that in some instances idiopathic myocardial hypertrophy occurs in several members of one family.[21–24] Such a familial occurrence was observed in only one of our patients. The pathologic and clinical findings do not permit distinction between these cases and those in which there is clearly no family history of cardiac disease of a similar type.

One must consider the possibility that chronic myocarditis could be responsible for the cardiac hypertrophy in our patients.[8, 25] It is difficult to believe that an inflammatory process could account for the marked cardiac hypertrophy seen in our subjects in the absence of either an infiltration of inflammatory cells or extensive myocardial fibrosis. Our patients, unlike those with isolated myocarditis, showed occasional small clusters of lymphocytes but no other cellular exudate.

Several of the patients in our group were alcoholic, and one must consider whether alcoholism is a factor in idiopathic cardiac enlargement. Myocardial damage has been produced by alcohol experimentally.[26] Gould[27] mentions the "beer drinker's heart" in human subjects but related the pathologic changes to the state of nutrition. Some of our patients had idiopathic cardiac hypertrophy in childhood, thus eliminating alcoholism as a cause of heart disease in all of these patients. Recently Gillanders[28, 29] has proposed that malnutrition or vitamin deficiency is the basic responsible factor in some instances for cardiomyopathy in the African. Idiopathic cardiomegaly, however, has been observed in very well nourished patients. The experience gained from clinical and necropsy studies in prison and in concentration camps has shown that atrophic rather than hypertrophic hearts were the rule in severe malnutrition.[30] One could also raise the question that some of these patients may have chronic beriberi heart disease. The studies of Rowlands and Vilter[2] and of Griffith[31] failed to demonstrate that beriberi would result in specific permanent pathologic alterations in the myocardium. Since four of our patients had nutritional cirrhosis of the liver, one must consider whether this could be directly or indirectly responsible for the myocardial hypertrophy and heart failure. Wuhrmann and others have suggested that protein deficiency may be responsible for cardiac abnormalities found in nutritional cirrhosis.[10, 28, 29, 32] There are many other factors, however, in nutritional cirrhosis that may be responsible for impairment of cardiac function: anemia, vascular shunts, high output hyperdynamic states, increased plasma volume, and vitamin deficiencies.[32–37]

An increased incidence of idiopathic cardiomegaly in nutritional cirrhosis was found by Lunseth, Olmstead, and Abboud[37] who described 12 instances of idiopathic cardiac enlargement in 108 patients dying of portal cirrhosis. These authors postulated that the cardiac enlargement was related to the increased cardiac output often found in portal cirrhosis.[33, 34]

One patient in our group of 18 (no. 4) developed congestive heart failure for the first time during the early postpartum period, raising the question of postpartum myocardosis.[38–40] She did not show evidence of pulmonary embolism, which may explain some instances of postpartum heart disease as indicated by Burchell,[41] nor did she have evidence of hypertension to explain the heart failure, which may explain others.[40] Whether or not postpartum heart disease is an entity or represents a coincidental development of heart failure in a patient with antecedent idiopathic cardiac enlargement remains in doubt.

The mechanism responsible for the cardiomegaly in primary myocardial disease remains obscure. It is possible that in some instances the pathogenesis is related to primary functional metabolic myocardial impairments, with dilatation and subsequent hypertrophy.[42] It is possible that a disorder of the energy production-release mechanism of the heart as a result of disturbance of an enzyme system with or without recognizable liver disease could be a mechanism producing cardiac enlargement and failure in some instances.

Summary

This study describes 18 patients from the University of Cincinnati Hospitals who died of congestive heart failure without clinical or pathologic evidence of a primary cause.

Clinical features. Their ages were from 18 months to 68 years at death. Fourteen were male and four female; 11 were white and seven were Negro. Seven patients had heart failure for 5 years or more; three had heart failure for over 10 years. Seven patients were alcoholic and three had nutritional cirrhosis. Transient mitral or tricuspid systolic murmurs and apical protodiastolic gallop rhythms were common. Atrial fibrillation was present in six patients. The electrocardiograms revealed abnormal left axis deviation in three and left bundle-branch block in two.

Right heart catheterization was performed in four of these patients and showed low cardiac output, increased arteriovenous oxygen difference, and elevation of pulmonary arterial, pulmonary wedge, right ventricular diastolic, and right atrial pressures.

Pathologic features. Heart weights were over 500 Gm. in 13 patients; all 18 had left ventricular hypertrophy. Mural thrombi were present in 10; six had pulmonary emboli and three had systemic arterial emboli. One patient had gross myocardial scarring; only two had small accumulations of inflammatory cells in the myocardium. Ten had focal increase of elastic tissue.

Primary myocardial disease may simulate coronary artery disease because of the abnormal electrocardiogram; it may simulate hypertensive heart disease because of elevation of diastolic blood pressure during heart failure in some patients; it may simulate pericardial effusion because of the poor cardiac pulsations, narrow pulse pressure, and paradoxical pulse. It may simulate rheumatic heart disease because of the apical systolic and diastolic murmurs, left atrial enlargement, and presence of Kerley lines. The cause is unknown. Only one patient in this group had a familial history of similar heart disease.

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References

1. Blankenhorn, M. A., and Gall, E. A.: Myocarditis and myocardosis. Circulation 13: 217, 1956.
2. Rowlands, D. T., and Vilter, C. F.: A study of cardiac stigmata in prolonged human thiamine deficiency. Circulation 21: 4, 1960.

3. FRIIS, T.: Studies on Sahli's high pressure stasis. Acta med. scandinav. 132: 181, 1948.
4. SAHLI, H.: Verkandl. Deutsch. Kong inn. Med. 19: 45, 1901. Cited by Friis.[3]
5. FRIEDBERG, C. K.: Diseases of the Heart. Ed. 2. Philadelphia, W. B. Saunders Company, 1956. p. 163.
6. FISHBERG, A. M.: Hypertension and Nephritis. Philadelphia, Lea and Febiger, 1954, p. 789.
7. WOOD, P.: Diseases of the Heart and Circulation. Eyre and Spottiswoode, London, 1957.
8. KLINE, I. K., AND SAPHIR, O.: Chronic pernicious myocarditis. Am. Heart J. 59: 681, 1960.
9. THOMAS, W. A., RANDEL, R. V., BLAND, E. F., AND CASTLEMAN, B.: Endocardial fibroelastosis—a factor in heart disease of obscure origin. New England J. Med. 251: 327, 1954.
10. SPODICK, D. M., AND LITTMAN, D.: Idiopathic myocardial hypertrophy. Am. J. Cardiol. 1: 610, 1958.
11. ELSTER, K. S., TUCHMAN, L. R., AND HORN, H.: Cardiac hypertrophy and insufficiency of unknown origin. Am. J. Med. 18: 900, 1955.
12. ELSTER, S. K., TUCHMAN, L. R., AND HORN, H.: Myocardial hypertrophy of unknown origin. Bull. New York Acad. Med. 31: 475, 1955.
13. SELZER, A., AND MCGAUGHEY, D. J.: Hemodynamic patterns in chronic cardiac failure. Am. J. Med. 28: 337, 1960.
14. BALCHUM, O. J., MCCORD, M. C., AND BLOUNT, S. G.: The clinical and hemodynamic pattern in non-specific myocarditis: A comparison with other entities also impairing myocardial efficiency. Am. Heart J. 52: 430, 1956.
15. LYNFIELD, J., GASUL, B. M., LUAN, L. L., AND DILLON, R. F.: Right and left heart catheterization and angiocardiographic findings in idiopathic cardiac hypertrophy with endocardial fibroelastosis. Circulation 21: 386, 1960.
16. LEVY, R. L., AND VON GLAHN, W. C.: Cardiac hypertrophy of unknown cause. Am. Heart J. 28: 714, 1944.
17. DAVIES, N. J. P.: Some consideration regarding obscure disease affecting the mural endocardium. Am. Heart J. 59: 600, 1960.
18. BLACK-SCHAFFER, B., AND TURNER, M. E.: Hyperplastic infantile cardiomegaly. A form of idiopathic hypertrophy with or without endocardial fibroelastosis. Am. J. Path. 34: 745, 1958.
19. BLACK-SCHAFFER, B.: Infantile endocardial fibroelastosis. A.M.A. Arch. Path. 63: 281, 1957.
20. SCOTTI, T. M.: Basophilic (mucinous) degeneration of the myocardium. Am. J. Clin. Path. 25: 994, 1955.
21. EVANS, W.: Familial cardiomegaly. Brit. Heart J. 11: 68, 1949.
22. LAMBERT, E. C., AND VLAD, P.: Primary Endomyocardial Diseases. The Pediatric Clinics of North America 5: 1057, 1958.
23. CAMPBELL, M., AND TURNER-WARWICK, M.: Two more families with cardiomegaly. Brit. Heart J. 18: 393, 1956.
24. BRIGDEN, W.: Uncommon myocardial disease. The non-coronary cardiomyopathies. Lancet 2: 1179 and 1243, 1957.
25. SAPHIR, O.: Myocarditis. Arch. Path. 33: 88, 1942.
26. FOLLIS, R.: The Pathology of Nutritional Diseases. Springfield, Illinois, Charles C Thomas, Publisher, 1948.
27. GOULD, S. E.: Pathology of the Heart. Springfield, Ill. Charles C Thomas, Publisher, 1953.
28. GILLANDERS, A. D.: Nutritional heart diseases. Brit. Heart J. 13: 177, 1951.
29. HIGGESIN, I., GILLANDERS, A. D., AND MURRAY, J. F.: The heart in chronic malnutrition. Brit. Heart J. 14: 213, 1952.
30. ELLIS, L. B.: Electrocardiographic abnormalities in severe malnutrition. Brit. Heart J. 8: 53, 1946.
31. GRIFFITH, R. L.: Condition of the heart following beriberi and malnutrition. A.M.A. Arch. Int. Med. 89: 743, 1952.
32. WUHRMANN, F.: Myocardosis. Zurich, Beno Swabe, 1956.
33. SHERLOCK, S.: Idiopathic cardiomegaly. Brit. M. J. 1: 945, 1960.
34. MURRAY, J. F., DAWSON, A. M., AND SHERLOCK, S.: Circulatory changes in chronic liver disease. Am. J. Med. 24: 358, 1958.
35. CALABREZI, P., AND ABELMANN, W. H.: Portocaval and porto-pulmonary anastomoses in Laennec's cirrhosis and in heart failure. J. Clin. Invest. 36: 1257, 1957.
36. OPPENHEIM, M.: Myocardosis in liver cirrhosis. Schwiez. Med. Wchnschr. 80: 795, 1950.
37. LUNSETH, J. H., OLMSTEAD, E. G., AND ABBOUD, F.: A study of heart disease in one hundred eight hospitalized patients dying with portal cirrhosis. A.M.A. Arch. Int. Med. 102: 405, 1958.
38. WOOLFORD, R. M.: Postpartum myocardosis. Ohio M. J. 48: 924, 1952.
39. BLANKENHORN, M. A.: Effect of vitamin deficiency on the heart and circulation. Circulation 11: 288, 1955.
40. BENCHIMOL, A. B., CARNEIRO, R. [illegible], AND SCHLESINGER, P.: Postpartum heart disease. Brit. Heart J. 21: 89, 1959.
41. BURCHELL, H. B.: Unusual cause of heart failure. Circulation 21: 436, 1960.
42. GRANT, R. P.: Aspects of cardiac hypertrophy. Am. Heart J. 46: 154, 1953.

Aortic Stenosis

Correlations between Pressure Gradient and Left Ventricular Angiocardiography

By VIKING OLOV BJÖRK, M.D., INGEMAR CULLHED, M.D., AND HERMAN LODIN, M.D.

IN THE STUDY of hemodynamics in aortic stenosis until the last decade more or less indirect methods were used, such as electrocardiography and phonocardiography, and direct and indirect pulse tracings. At best the results would confirm a clinical diagnosis but often were of little help in the surgical evaluation of the valvular defect.

Only after the introduction of left-sided heart catheterization with pressure measurements in the left ventricle, by the transthoracic or transbronchial left atrial routes[1, 2] or percutaneous left ventricular puncture,[3] can the aortic stenosis be evaluated with respect to the systolic pressure gradient.

Thoracic aortography can give valuable information in aortic stenosis concerning the mobility of the aortic cusps and the degree of post-stenotic aortic dilatation[4] but does not reveal subaortic stenosis. Thoracic aortography is the routine method in assessing aortic regurgitation.[5]

Aortic catheterization may be extended to the left ventricle,[6, 7] where contrast injection may be done.[8] This method carries the danger of damaging an aortic cusp or obstructing a coronary ostium.[6, 9] Further, the roentgenologic study of the mobility of the aortic leaflets is disturbed by the presence of the catheter, and in tight stenosis the catheter adds to the obstruction and artificially exaggerates the systolic pressure in the ventricle.

We have in the last years performed percutaneous puncture of the left ventricle with contrast injection in more than 120 cases. The value of left ventricular angiocardiography in the diagnosis of valvular heart disease was shown early.[10, 11] It is the aim of this paper to discuss the correlations between the pressure measurements and the findings at the left ventricular angiocardiography in aortic stenosis.

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Material and Methods

The material consists of 36 patients with aortic stenosis of whom 21 had a pressure gradient over the aortic orifice. The patient lies supine, and with the caudal part of the thorax at some distance from the lateral film (see below). A thin polythene catheter, 10 to 15 cm. long, was introduced percutaneously into a peripheral artery, usually the left femoral artery. The left ventricle was punctured under local anesthesia as suggested by Brock.[3] The catheter and the puncture needle were connected each to a strain-gage electromanometer,* with the anterior axillary line as reference level. The pressure curves were recorded on a direct-writing four-channel oscillograph,* together with a standard limb-lead electrocardiogram and the x-ray exposures. On a single-beam cathode-ray oscilloscope,* the electrocardiogram or a pressure curve was continually observed.

On undamped curves the systolic pressures were determined in the ventricle and the artery. From these values the gradient between the peak systolic pressures was calculated. After the position of the needle in the ventricle was controlled by observation of the ventricular pressure curve when the direction of the needle was altered, 1 ml. of 76 per cent "Urografin" per Kg. of body weight was injected, an electrocardiogram being run at the same time. Six frames per second (maximum exposure time 0.03 second) were exposed in two planes during inspiration. During and immediately after the injection the carotid arteries were compressed in order to reduce the flow of contrast material to the brain.

After the withdrawal of the needle an electrocardiogram and a chest x-ray were taken to look for signs of cardiac tamponade or pneumothorax.

*Manufactured by Elema, Inc., Stockholm, Sweden.

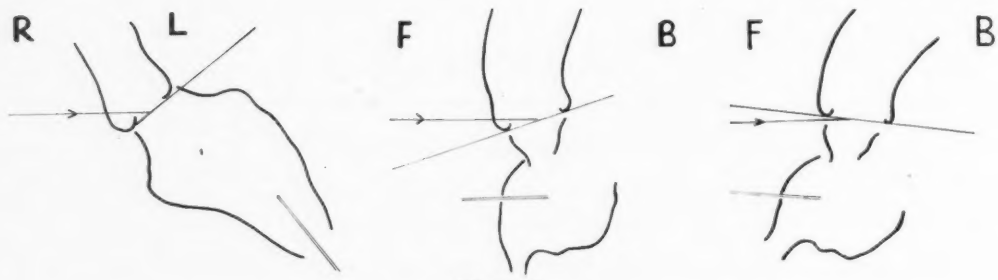

Figure 1

Schematic drawings illustrating the inclination of the valvular plane: Left, in the frontal, center and right, in the lateral projection. F, front; B, back; R, right; L, left. The direction of the beam: (→) The needle:———

We have encountered two fatal complications among our first 120 left ventricular punctures.[12] In a 55-year-old man cardiac tamponade occurred and in a 9-month-old boy the contrast was injected into the myocardium. A detailed report of our minor and major complications is under preparation.

Roentgenologic Aspects

In the ideal roentgen visualization of the aortic orifice the beams should be parallel with the valve plane. In true frontal and lateral projections, however, the incident beam generally forms an angle with that plane (fig. 1). This disadvantage can, however, to some extent be reduced by adjusting the position of the patient or the tubes to bring the beams more parallel to the valve plane.

The position of the lateral tube or the patient should be arranged so that the beam falls in a somewhat caudo-cranial direction; the more so, the more transverse is the position of the heart. Adjustment of the frontal tube, however, has little effect, since the angle between the valve plane and the vertical beam (fig. 1) generally is small and since the valve plane may be inclined either cranially or caudally. The orientation of the valve plane thus cannot be exactly predicted.

In assessing the thickness and mobility of the individual cusps, it is essential that the beam be directed along the cusp and its base "tangentially" (fig. 2). It is impossible to get more than one of the three cusps in an ideal position with use of two planes at right angles to each other. In a true lateral projection a "tangential" picture is obtained of the right coronary cusp, whereas in pure frontal and lateral projections a more oblique view is obtained of the other two cusps.

Accordingly we have been using true frontal and lateral projections, the inferior part of the thorax being at a slight distance from the vertical film plane.

Owing to this arrangement it may be necessary to tolerate projections that are at times highly unsatisfactory, rendering difficult the assessment of the morphology of the aortic orifice and the mobility of the cusps. Thus two or even all of the cusps may be shown in some degree of "oblique" projection, and it may be incorrectly assumed that the mobility of the cusps and caliber of the aortic orifice are reduced. Further, the valve plane may be completely masked in the lateral projection by an enlarged left ventricle when there is transverse position of the heart. With use of two planes at right angles to each other, however, some of the difficulties are eliminated, the assessment of the orifice being based on a comparison between the two planes.

The *normal orifice* is characterized by thin scarcely visible cusps, which open fully in systole and close tightly in diastole.

The *diagnosis of aortic stenosis* is made on the grounds of the thickness and mobility of the cusps, the caliber of the orifice, the rate of contrast flow through the orifice, the appearance of the ascending aorta, and the

Table 1

Correlations between the Pressure Gradient in Millimeters of Mercury over the Aortic Orifice and the Electrocardiographic Changes in leads V_1 to V_6

Pressure gradient in mm. Hg	S-T depression and negative T waves	Diagnosis	Femoral artery pressure	Systolic and end-diastolic left ventricular pressure
128	—	AS	120/75	248/15
105	+	AS MI	100/65	205/10
102	+	AS MI	140/60	242/20
100	+	AS MS TS	105/80	200/0
89	+	AS MS MI AI	188/84*	277/20
80	+	AI AS	150/73	230/13
80†	+	AS	115/49	195/6
75	—	AS MS	110/62	185/15
52	+	AS AI MI	142/64	194/32
50	—	AS MI MS AI	190/72	240/20
40	—	MS AS MI AI	118/70	158/0
40	—	MS AS AI	125/95	165/0
32	—	AS	125/72	157/15
30	—	AS	140/84	170/14
27	—	AS	137/59	164/0
25	—	AS MS	185/93	210/15
20	—	AS	135/64	156/4
20	—	AI AS	210/84	230/7
15	—	AI AS	185/80	200/5
12	—	MS AS	130/55	142/0
8	—	MS AS AI	159/86	167/8

*Brachial artery pressure.

†In this case no angiocardiogram was obtained. The patient died in connection with the puncture and was reported recently.[12]

(AS = aortic stenosis, AI = aortic insufficiency, etc.)

emptying capacity of the left ventricle and the thickness of its wall.

In estimating the thickness of the cusps, care must be taken to measure only cusps that are seen in "tangential" view, or misleading figures will be obtained.

The mobility of the cusps is estimated by observing their position during different phases of the cardiac cycle, regard being paid to any disturbances of rhythm and the rate of flow. The rate of flow may be so slow, for example in marked mitral stenosis and mitral incompetence, that it is insufficient to open the valves fully, especially if the aortic cusps are thickened. If the rate of flow is neglected, therefore, a "morphologic" stenosis may be diagnosed when in fact the cusps are normal or thickened but not fused.

In many cases of stenosis a typical dome is seen. The caliber of the orifice is assessed with greatest accuracy if there is a jet. In many cases, however, the caliber may be measurable in only one plane, or not at all, because the orifice is eccentric on the dome and the incident beam therefore does not meet it tangentially.

The degree of stenosis when the orifice cannot be measured exactly may to a certain extent be assessed by estimating the rate of the flow and the degree of post-stenotic dilatation of the ascending aorta. If other causes of delayed flow can be excluded, incomplete mixture of contrast medium and blood in the ascending aorta indicates grave stenosis. In cases of pure stenosis conclusions can even be drawn from the thickness of the ventricular wall which is measured in diastole above the apex. The emptying time of the ventricle after the completion of the injection, in relation to the number of ventricular contrac-

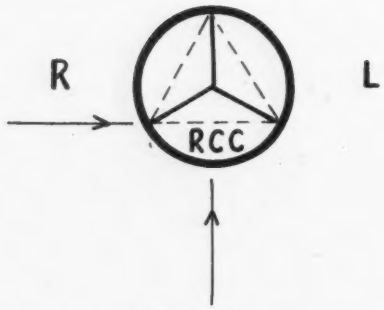

Figure 2

Schematic drawing illustrating the relations between the cusps and the incidence of the beam. In the lateral projection the right coronary cusp meets the beam ideally. An oblique view is obtained of the two other cusps in both projections. RCC, right coronary cusp; R, right; L, left. The direction of the beam (→)

tions, will, in the absence of a mitral lesion and aortic insufficiency, give an idea of the residual blood.

Results

Undamped pressure curves were obtained in all cases but two. These patients (cases no. 6 and 31) suffered from obliterating, probably thromboembolic aortic disease. The femoral pulses were absent in one and weak in the other patient. This source or error in the determination of the pressure gradient should be considered in the elder patients.

The pressure gradient in four cases was again measured during operation, prior to valvulotomy. A reasonable correlation was found with the preoperative values, the difference being −10, +13, +11, and −58 mm. Hg. The significant lower value in the last case (no. 100) may be due to altered hemodynamics, as the operation was performed in hypothermia and extracorporeal circulation. The remaining gradient, 70 mm., was reduced to 0 mm. through the operation. Other authors, too, have found a good correlation between the pressure gradients before and during surgery.[3, 13, 14]

In normal cases as well as in aortic stenosis there is usually a higher systolic pressure in the femoral arteries than in the central aorta.[15–17] Even a small positive systolic pressure gradient between the left ventricle and the femoral artery will thus probably be due to some degree of stenosis. Because of the jet effect pressure measurements just distal to the aortic valve will differ considerably according to the situation of the tip of the catheter.[18–20] It should thus be safer to measure the pressure in the femoral artery.

In the following our search for different correlations with the pressure gradient is related. We wish to emphasize once more that "pressure gradient" means the gradient between the left ventricular and the peripheral artery pressures.

Table 2

Correlations between the Gradient and the Incidence of Calcifications

Pressure gradient in mm. Hg	Number of cases	Number with calcifications	Mean age	
			without calcifications	with calcifications
128-52	8	7	29	49
50-25	7	4	32	42
20- 8	4	1	42	46
0	10	1	41	48

Table 3

The Pressure Gradient Correlated with the Left Ventricular Wall Thickness

Pressure gradient in mm. Hg	Number of cases	Thickness of ventricle in mm.	
		mean	range
128-52	8	16	12-20
50-25	7	14	9-25
20- 8	5	11	8-15
0	15	12	6-25

Correlations between the Gradient and the Electrocardiographic Changes

The material was grouped according to the pressure gradient, (table 1). All cases but one, with a gradient of at least 80 mm. Hg show S-T depression and T-wave negativity in at least two of leads V_4, V_5, and V_6. This is in general agreement with Fleming et al.,[21] although the exceptional case with a gradient of 128 mm. Hg (the diagnosis was verified at open-heart surgery) shows the possibility of severe aortic stenosis with an essentially normal electrocardiogram. This point was also made by Matthews et al.[22] The same electro-

Table 4

The Pressure Gradient Correlated with the Size of the Aortic Orifice

Pressure gradient in mm. Hg	Number of cases	Diameter in mm.	
		mean	range
105-52	7	8	3-15
50- 8	8	10	5-15
0	14	11	8-15

cardiographic findings were found in a case with a gradient of only 52 mm., with severe combined aortic valvular disease and left heart failure. Of the 15 cases with aortic stenosis without a pressure gradient only one had the same electrocardiographic picture, a 40-year-old man with aortic stenosis and insufficiency and mitral insufficiency.

Correlation between the Gradient and the Incidence of Aortic Valvular Calcification

The presence of calcifications in the material was investigated by means of tomography, which was performed in 29 of the 36 cases. When the incidence of calcifications was correlated to the pressure gradients (table 2), a higher incidence was found in those with a larger gradient. In the different groups the cases with calcification were found in the older patients.

Correlation between the Pressure Gradient and the Degree of Left Ventricular Hypertrophy

On the angiocardiograms the thickness of the left ventricle in diastole was measured as an index of the degree of hypertrophy (table 3).

Since the groups are small, very limited conclusions can be drawn. There seems to be a positive correlation, however, between the gradient and the degree of left ventricular hypertrophy, as would be anticipated.

Correlation between the Pressure Gradient and the Left Ventricular End-Systolic Volume

The volume of the contrast-filled ventricular cavity at the end of systole was assessed on the angiocardiograms. No correlation was found between the gradient and this volume. Nor was any correlation found between this volume and the total heart volume, expressed in milliliters per square meter of body surface area. The degree of arrhythmia induced by the contrast injection could not be shown to influence the magnitude of the residual volume.

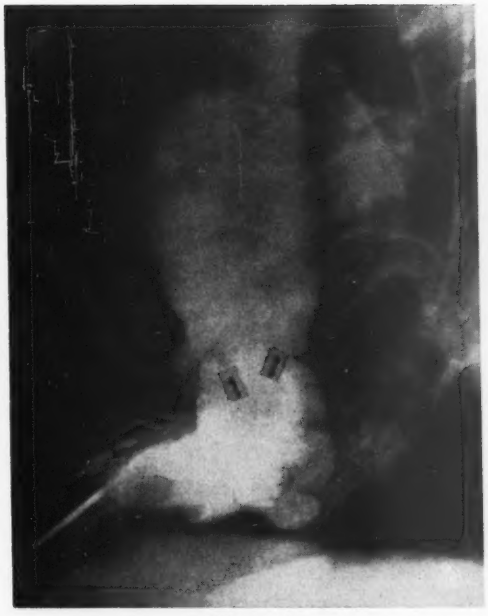

Figure 3

(G. K.) Aortic valvular stenosis. Angiocardiogram after ventricular puncture. Ventricular systole. Lateral plane. Typical aortic stenosis with thickened cusps. The enlarged left ventricle superimposes partly the orifice. Great dilatation of the ascending aorta.

Correlation between the Gradient and the Degree of Stenosis

The normal aortic orifice has a diameter of about 2.6 cm.[14] The diameter in vivo can be estimated indirectly in pure aortic stenosis according to the formulas introduced by Gorlin.[23] More directly the diameter can be determined during open-heart surgery, though palpation may overestimate the width of the ostium.[24] With due regard to the limitations discussed earlier in this paper we have tried to measure the diameter of the aortic orifice on the angiocardiograms. This was possible in 29 cases, and these were grouped according to the pressure gradient (table 4). The orifice is smaller in the cases with the largest gra-

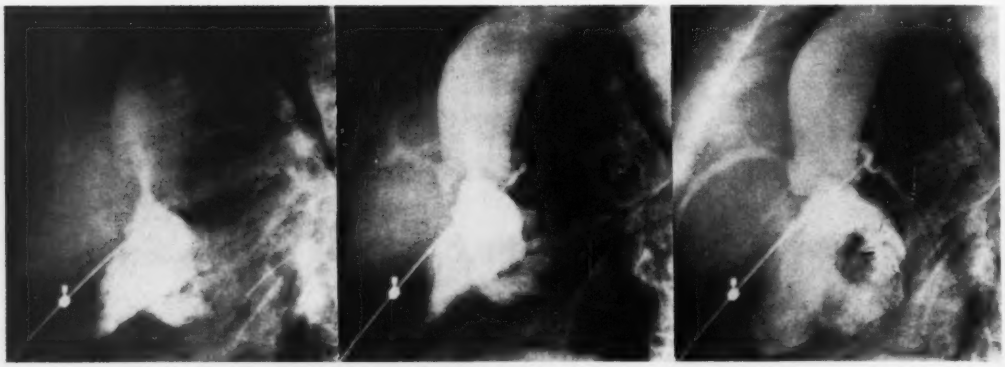

Figure 4

(M. J.) Aortic valvular stenosis + mitral stenosis. Angiocardiograms after ventricular puncture. Ventricular systole, (left, center) lateral plane, ventricular diastole, (right) lateral plane. Typical aortic stenosis with a 3-mm. broad jet through the orifice. The jet is eccentric, the contrast stream directed against the anterior aortic wall (left). The cusps are very thick (center) and practically without any mobility (right). Slight dilatation of the middle part of the ascending aorta. Typical mitral dome[26] (right): mitral stenosis.

dients: in this group only one case had a diameter of over 10 mm. That case had a gradient of 102 mm. with a ventricular pressure of 240/20 mm. Hg in the absence of any clinically significant aortic incompetence.

There was no correlation between the gradient and the thickness of the aortic cusps, which in all cases measured 2 to 4 mm. The mobility of the cusps was good in only four of 20 cases with a pressure gradient, contrasted with the good mobility in eight of 15 cases without gradient.

No correlations were found between the gradient and the heart volume, the left ventricular emptying time or the physical working capacity, as measured on an ergometer cycle in kilograms per meter per minute.

The findings in four cases of aortic stenosis are presented as representative examples.

Case Reports

Case 1

G. K., a 39-year-old man (201024/59). No rheumatic fever. For 2 or 3 years dyspnea and dizziness on work. Clinically he was classified as isolated aortic stenosis. Right heart catheterization: normal pressure values in rest and at work. Electrocardiogram: no definite signs of hypertrophy. Chest radiogram revealed a normal-sized heart (340 ml./M.^{2} BSA), on tomography rather extensive intracardiac calcifications were seen in the aortic valvular region. On left ventricular puncture a pressure gradient over the aortic orifice of 128 mm. Hg was detected. Left ventricular angiocardiogram: see figure 3. The patient was operated upon with the aid of deep hypothermia (24 C.) and extracorporeal circulation. The noncoronary and the fused right and left coronary cusps were found heavily calcified, leaving a long but narrow passage for the blood stream. By curettage the noncoronary cusp could be decalcified and mobilized, resulting in elimination of the pressure gradient, as measured during surgery. No attempt at valvulotomy was regarded as possible because the mobility would not be influenced. When the patient left the hospital 5 weeks after the operation he was subjectively better and had less calcifications on tomography. The patient died 2 months later of a brain embolism from an incisional aortic aneurysm.

Case 2

M. J., a 45-year-old woman (140921/58). Rheumatic fever when 19 years old. For the last 5 years decompensated—grade III (New York Heart Association). She was admitted for the first time in 1957. A tricuspid and mitral stenosis was diagnosed and later was operated upon.[25] For the first half year she felt better but then her symptoms came back and she was again admitted in 1958. The clinical diagnosis now became aortic, mitral, and tricuspid stenosis, possibly mitral regurgitation. Right heart catheterization revealed moderate pulmonary hypertension

and a diastolic gradient between the right atrium and ventricle. Electrocardiogram: right axis deviation, no ventricular hypertrophy. Chest radiogram: heart size 1080 ml./M.^{2} BSA. Tomography: mitral and aortic calcifications. On left ventricular puncture a systolic pressure gradient of 100 mm. Hg was found. The angiocardiogram (fig. 4) visualized a valvular aortic stenosis. On reoperation a transventricular dilatation of the aortic and mitral valves was done. However, a rupture of the aortic valve occurred, resulting in severe aortic regurgitation, which overburdened the heart. The autopsy confirmed the preoperative diagnosis.

Case 3

R. E., a 20-year-old man (390321/59). No rheumatic fever. A murmur heard since the early school years. Slight symptoms on exercise (grade I). Clinical diagnosis: isolated aortic stenosis. Electrocardiogram: normal. Chest radiogram: heart size 400 ml./M.^{2} BSA. Tomography: no calcifications. Left ventricular puncture: valvular aortic stenosis (fig. 5) with a pressure gradient of 32 mm. Hg. So far operation has not been advised.

Case 4

R. J., a 40-year-old woman (180613/58). Rheumatic fever when 34 years old, since that increasingly decompensated, functionally grade III. The clinical diagnosis was aortic and mitral stenosis. Right heart catheterization revealed definite pulmonary hypertension, Electrocardiogram: left atrial enlargement, but no signs of ventricular hypertrophy. Chest radiogram: heart size 495 ml./M.^{2} BSA. Tomography: no calcifications. Left ventricular puncture was performed. There was no pressure gradient but the angiocardiograms (fig. 6) showed a valvular aortic stenosis with fused but mobile cusps. At operation the mitral stenosis was very tight, open only for the tip of the finger. A transventricular dilatation was performed, first of the mitral valve to about 1½ fingerbreadths, and then of the aortic valve, which offered a hard resistance to the instrument. With some force the valve could be dilated to about 2 fingerbreadths. After the first postoperative week in a respirator the patient made a good recovery and left the hospital after 7 weeks.

Discussion

Leonardo da Vinci, as quoted by McMillan,[24] has shown the triangular form of the normal aortic orifice. The internal diameter of this orifice averages 2.6 cm., which makes an area of about 3 cm.^{2} No hemodynamic changes occur until the orifice is reduced to at least one quarter,[18] corresponding to a

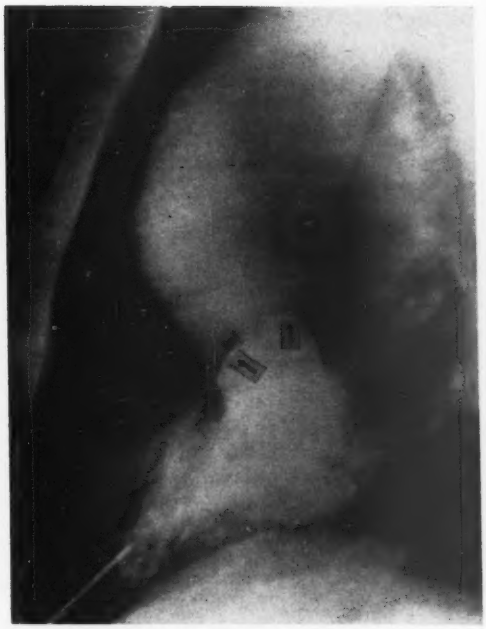

Figure 5

(R. E.) Aortic valvular stenosis. Angiocardiogram after ventricular puncture. Ventricular systole. Lateral plane. Typical aortic stenosis with dome formation of the thickened aortic cusps. The orifice is about 1.5 cm. in this plane. The ascending aorta, especially the middle part of it, is extremely dilated. Medionecrosis cystica?

diameter of about 10 mm. In isolated aortic stenosis the valve area may be estimated when the rate and magnitude of flow across the valve are known. This is possible if the pressures on both sides of the valve are determined at the same time as the cardiac output. In coexisting aortic regurgitation the total left ventricular stroke volume cannot be determined and thus the valve area during systole cannot be assessed either. In spite of insignificant stenosis a large systolic pressure gradient will occur in aortic regurgitation,[27] due to the large systolic flow. However, in acute dog experiments Moscovitz et al.[28] obtained no systolic pressure gradient in aortic regurgitation.

On the other hand, in mitral stenosis and insufficiency the aortic flow will be diminished, as in left ventricular failure. When

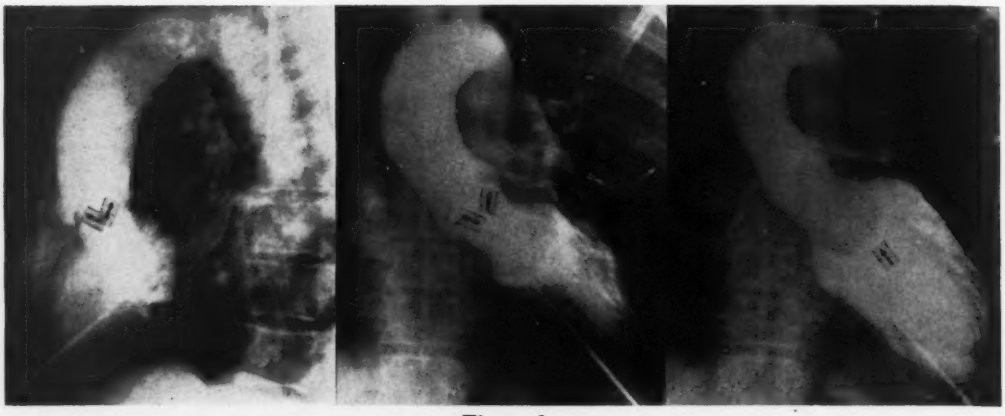

Figure 6

(R. J.) Aortic valvular stenosis + mitral stenosis. Angiocardiograms after ventricular puncture. Ventricular systole: (left) lateral plane, (center) frontal plane. Ventricular diastole: (right) frontal plane. Typical aortic stenosis with thick cusps and dome formation in both planes. The orifice is about 1.5 cm. in diameter. The aortic cusps have a good mobility. Slight dilatation of the middle part of the ascending aorta. The free borders of the mitral leaflets are thickened (left) and in ventricular diastole a typical mitral dome is seen (right), causing a defect in the ventricular contrast: mitral stenosis.

significant aortic stenosis exists, the diminished flow will give only a small gradient.

From a practical point of view Brock[29] and Wood[14] stated that a pressure gradient over the aortic orifice of at least 50 mm. points to a significant aortic stenosis. In coexisting mitral stenosis or aortic regurgitation the gradient should exceed 25 or 100 mm. respectively.

The combination in left ventricular puncture of pressure measurement and left ventricular angiocardiography has not been reported earlier in the study of aortic stenosis. Cregg et al.[30] mentioned "the excellent visualization of the aortic mitral valves," but reported no case of aortic stenosis. Recently Connolly[31] performed pressure measurements in aortic stenosis and mentioned contrast injection. No results were given, however.

Our material of 36 cases is rather heterogeneous, with six cases of isolated aortic stenosis and 30 cases of different combinations of valvular diseases. In this report we have chosen to present the whole material together, grouped according to the pressure gradient, since the different diagnostic subgroups would otherwise be very small.

With one exception the gradient was found to correlate well with the T-wave negativity over the left ventricle. The same applies to the degree of aortic valvular calcifications and, though less marked, to the size of the orifice and to the ventricular wall thickness. In estimations of the size of the orifice due attention must be paid to the risk of overdiagnosis by underestimating the width, if due to low stroke volume (e.g., in mitral insufficiency or stenosis) or to unsatisfactory, oblique projections.

Probably hemodynamic changes may occur even before the aortic ostium is reduced to one fourth of the normal area, i.e., to a diameter of about 10 mm. Our two cases with isolated aortic stenosis and gradients, respectively 20 and 27 mm. Hg, had ostium widths of 15 and 12 to 13 mm., respectively, and these are minimum measurements. However, these cases were young men with only slight symptoms and have so far not been operated upon.

On the other hand a tight aortic stenosis may exist without any pressure gradient, if combined with mitral valvular disease or in left ventricular failure. In this material two

cases with mitral and aortic stenosis without gradient had aortic ostium widths of 8 and 10 mm. Both cases were operated upon with closed transventricular dilatation of both valves. The aortic valves made a tough resistance to the instrument in both cases, but a successful dilatation was performed. So far no case without a gradient has been operated upon with open technic.

It is thus our impression that left ventricular angiocardiography is a valuable addition to the technic of left ventricular puncture, in the study of aortic stenosis. Especially in combined valvular disease we think it may sometimes be of vital importance in order to detect preoperatively and to grade an aortic stenosis. The absence of a gradient at rest in these cases is probably due to lessened diastolic filling. Perhaps more information could be gained by measuring the ventricular pressure at rest and graded exercise.

The value of left ventricular angiocardiography in the diagnosis of subvalvular aortic stenosis was recently reported.[32] The same should apply to the diagnosis of supraaortic stenosis and a coexistent aortic coaretation.

Post-stenotic aortic dilatation is usual in valvular aortic stenosis and can be detected in chest radiograms. A more exact outline may be obtained by contrast injection, as is shown in our case 3, where the considerable aortic dilatation awoke suspicions of medionecrosis cystica.[33]

Summary

In 36 cases of valvular heart disease with a clinical diagnosis of isolated or significant aortic stenosis we have performed percutaneous intercostal puncture of the left ventricle for pressure measurements and, in all but one case, left ventricular angiocardiography. The possible correlations between the pressure gradient and the angiocardiographic findings are discussed.

With the exception of the unsatisfactory angiocardiograms due to oblique projection of the valvular planes, valuable information was obtained regarding the degree of aortic stenosis. This was especially the case if the aortic stenosis was combined with mitral valve disease, resulting in a small or no systolic pressure gradient.

References

1. Björk, V. O. and Malmström, G.: Left heart catheterization. Circulation Research 2: 424, 1954.
2. Morrow, A. G., Braunwald, E., Haller, J. A., and Sharp, E. H.: Left atrial pressure pulse in mitral valve disease: A correlation of pressures obtained by transbronchial puncture with the valvular lesion. Circulation 16: 399, 1957.
3. Brock, R. C., Milstein, B. D., and Ross, D. N.: Percutaneous left ventricular puncture in the assessment of aortic stenosis. Thorax 11: 163, 1956.
4. Ödman, P., and Philipsson, J.: Aortic valvular diseases studied by percutaneous thoracic aortography. Acta radiol., Suppl. 172, 1958.
5. Castellanos, A., and Garcia, O.: The diagnosis of aortic insufficiency in the living subject and the cadaver by means of retrograde aortography. Rev. cubana Pediat. 25: 455, 1953 (see reference 4).
6. Zimmerman, H. A., Scott, R. W., and Becher, N. O.: Catheterization of the left heart in man. Circulation 1: 357, 1950.
7. Stampbach, O., and Joss, E.: Der Katheterismus des linken Herzens. Unter besonderer Berücksichtigung des retrograden arteriellen Weges. Cardiologia 35: 382, 1959.
8. Johnson, J. B., Lawlah, J. W., McFadden, F., and Dyer, Jr., J. F.: Thoracic aortography. Am. Heart J. 53: 40, 1957.
9. Johnson, B., and Logan, A.: Coronary artery catheterization during thoracic aortography. Brit. Heart J. 20: 411, 1958.
10. Ponsdomenech, E. R., and Nunez, V. B.: Heart puncture in man for diodrast visualization of the ventricular chambers and great arteries. Am. Heart J. 41: 643, 1951.
11. Nunez, V. B., and Ponsdomenech, E. R.: Heart puncture. II. Cardioangiography: Clinical and electrocardiographic results. Am. Heart J. 41: 855, 1951.
12. Björk, V. O. and Lodin, H.: Left heart catheterization with selective left atrial and ventricular angiocardiography in the diagnosis of mitral and aortic valvular disease. Progr. Cardiovas. Dis. 2: 116, 1959.
13. Greene, D. G., Sharp, J. T., Griffith, G. T., Bunell, I. L., and MacManus, J. E.: Surgical applications of anterior percutaneous left heart puncture. Surgery 43: 1, 1958.
14. Wood, P.: Aortic stenosis. Am. J. Cardiol. 1: 553, 1958.

15. KROEKER, E. J., AND WOOD, E. H.: Comparison of simultaneous recorded central and peripheral arterial pulses during rest, exercises and tilted position in man. Circulation Research 3: 623, 1955.
16. WRIGHT, J. L., TOSCANO-BARBOZA, E. AND BRANDENBURG, R. O.: Left ventricular and aortic pulses in aortic valvular disease. Proc. Staff Meet., Mayo Clin. 31: 120, 1956.
17. ROSHE, J., AND MORROW, A. G.: Central and femoral pulses in aortic valve disease. Am. Heart J. 55: 599, 1958.
18. WIGGERS, C. J.: Physiology in Health and Disease. Ed. 2. London, Henry Kimpton, 1937.
19. CASTENFORS, H., PORJÉ, I. G., AND RUDEWALD, B.: The hydrodynamics of aortic valve stenosis; experiments with a special model. Cardiologia 25: 37, 1954.
20. PORJÉ, I. G.: Hämodynamiken vid aortastenos. Opusc. Med. 2: 62, 1957.
21. FLEMING, P., AND GIBSON, R.: Percutaneous left ventricular puncture in the assessment of aortic stenosis. Thorax 12: 37, 1957.
22. MATTHEWS, M. B., MEDD, W. E., AND GORLIN, R.: Aortic stenosis: a clinical study. Brit. M. J. 2: 759, 1955.
23. GORLIN, R., AND GORLIN, S. G.: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am. Heart J. 41: 1, 1951.
24. MCMILLAN, I. K. R.: Aortic stenosis. A post-mortem cinephotographic study of valve action. Brit. Heart J. 17: 56, 1955.
25. CULLHED, I. AND MALERS, E.: Tricuspid-mitral stenosis. Acta Soc. med. upsalien 62: X, 1957.
26. BJÖRK, V. O., AND LODIN, H.: The evaluation of mitral stenosis with selective left ventricular angiocardiography. J. Thoracic Surg. 40: 17, 1960.
27. GORLIN, R., MCMILLAN, I. K. R., MEDD, W. E., MATTHEWS, M. B., AND DALEY, R.: Dynamics of the circulation in aortic valvular disease. Am. J. Med. 18: 855, 1955.
28. MOSCOWITZ, H. L., AND WILDER, R. J.: The pressure events of the cardiac cycle in the dog: Aortic valve lesions. Am. Heart J. 54: 572, 1957.
29. BROCK, R.: Surgical treatment of aortic stenosis. Brit. M. J. 1: 1019, 1957.
30. CREGG, H. A., SMITH, P. W., WILSON, C. W., AND BULL, J. W.: Cardioangiography. Radiology 65: 369, 1955.
31. CONNOLLY, J. E.: Left ventricular puncture in the assessment of aortic stenosis. J.A.M.A. 171: 160, 1959.
32. BJÖRK, V. O., JONSSON, B., AND NORDENSTRÖM, B.: Subaortic stenosis. Thorax 13: 201, 1958.
33. MCKUSICK, V. A., LOGUE, R. B., AND BAHNSON, H. T.: Association of aortic valvular disease and cystic medial necrosis of the ascending aorta: Report of four instances. Circulation 16: 188, 1957.

To the physician particularly a scientific discipline is an incalculable gift, which leavens his whole life, giving exactness to habits of thought and tempering the mind with that judicious faculty of distrust, which can alone, amid the uncertainty of practice, make him wise.—SIR WILLIAM OSLER. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 114.

The Value of Quinidine in the Prevention of Atrial Fibrillation after Mitral Valvuloplasty

By HARRISON BLACK, M.D., BERNARD LOWN, M.D., AND ANTHONY F. BARTHOLOMAY, S.D.

ATRIAL FIBRILLATION is the characteristic arrhythmia of the advanced stages of mitral stenosis, being present in 40 per cent of such cases. Paradoxically, mitral valve surgery, which relieves the obstruction and reduces the hemodynamic overload of the left atrium, frequently precipitates either transient or permanent atrial fibrillation. The reported incidence of this disorder after mitral operation ranges from 24 to 47 per cent.[1-6] In the patient with normal sinus rhythm undergoing mitral valve surgery atrial fibrillation thus constitutes the most common operative complication.

Physiologic studies clearly indicate that atrial fibrillation compromises cardiac function. Restoration of normal sinus rhythm has been shown to increase the cardiac output at rest and especially after exercise.[7-10] It has been observed that patients with atrial fibrillation have generally lower cardiac outputs, higher pulmonary vascular resistance, and higher left atrial and pulmonary arterial pressures than do patients with mitral stenosis in sinus rhythm.[11, 12] The ventricular rate in atrial fibrillation is unstable and prone to acceleration to more than 100 per minute. In some fully digitalized patients ventricular rates as high as 170 have been recorded following moderate exercise or administration of atropine.[13] Occasionally in the presence of this arrhythmia congestive failure cannot be controlled, even though the heart rate is slow, until normal sinus rhythm has been restored. It has furthermore been shown that atrial systole plays a role in closure of the atrioventricular valves.[14] Some degree of tricuspid insufficiency accompanies the development of atrial fibrillation in many patients.[15] Of greater clinical importance is the fact that this arrhythmia bears an etiologic relationship to cerebral and peripheral arterial embolization. Thus, the prevention of atrial fibrillation and its prompt conversion to a normal mechanism are sound clinical practice.

The present study had as its primary purpose the assessment of the effectiveness of quinidine in the prevention of postoperative atrial fibrillation. In addition, observations were made on the safety of using quinidine prophylactically during and following a cardiac operation and on the background factors that might predispose to this arrhythmia.

Materials and Methods

The investigation consisted of two phases, a retrospective and a prospective study.

Retrospective Study

The retrospective study consisted of analysis of the records of 255 patients in normal sinus rhythm who underwent mitral valvuloplasty at the Peter Bent Brigham Hospital. These patients were drawn from a larger series of 1,000 who were operated on in the Boston area and reported previously.[16] Of the 255 patients there were 226 who were classified as group III; in this category are included patients exhibiting severe progressive cardiac disability that has not yet reached the stage of the irreversible congestive failure or cardiac invaldism that characterizes group IV. The remaining 29 patients belonged in this latter category and are considered with a small group of similar patients in the prospective study. The major emphasis in the current investigation has centered on the group-III patients, since their larger number seemed more appropriate for statistical evaluation.

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*We are indebted to Dr. Dwight E. Harken for permission to use his patients in both the retrospective and prospective studies.

Table 1

Effect of Quinidine Prophylaxis on the Incidence of Atrial Fibrillation after Mitral Valvuloplasty in Group-III Patients.

	(Retrospective Study)		
	No. in NSR*	No. with PO-AF†	% PO-AF
Control	38	19	50
Quinidine	188	41	22

*Normal sinus rhythm.

†Postoperative atrial fibrillation.

In the retrospective series quinidine prophylaxis had been applied empirically when it was observed that there was a very high incidence of postoperative atrial fibrillation following mitral valvuloplasty. Thirty-eight of the group-III patients, most of them from the first part of the series who were among the earliest operated on for mitral stenosis, received no quinidine and served as controls. The remaining 188 group-III patients received this medication, beginning within 6 hours of the end of operation in the majority and administered in doses of 0.8 to 1.2 Gm. per day. In group IV 22 of the 29 patients received quinidine.

Prospective Study

In order to determine the effectiveness of quinidine prophylaxis under more controlled conditions a prospective study was also undertaken. For a period of 18 months all patients in normal sinus rhythm admitted to the Peter Bent Brigham, Mount Auburn, and Malden Hospitals on the Thoracic Surgical Services for mitral valvuloplasty were included. The group-III and group-IV patients were segregated and within each group the patients were paired as they were accepted for operation. To avoid bias and insure uniformity of decision a coin was tossed to determine which person should be assigned to the quinidine-treated group and which to the control (no quinidine) group.

All patients were digitalized preoperatively if not already receiving this drug.* In the therapy group, quinidine sulfate was given in 3 doses of 0.3 Gm. each, on the day prior to operation. On the day of operation and daily thereafter 0.3 Gm. was given every 6 hours, initially intramuscularly and thereafter by mouth.

Results

Retrospective Study

As shown in table 1, 50 per cent of the group-III patients in normal sinus rhythm preoperatively developed atrial fibrillation after operation. By contrast only 22.8 per cent of those receiving the drug manifested this arrhythmia. The difference is statistically highly significant with a p value of less than 0.001. Quinidine was equally effective whether the dose was 0.8 or 1.2 Gm. per day. There was indeed a lesser, though not significantly different, incidence of atrial fibrillation on the lower dose.

*Two in the control group did not receive digitalis; one fibrillated, one did not.

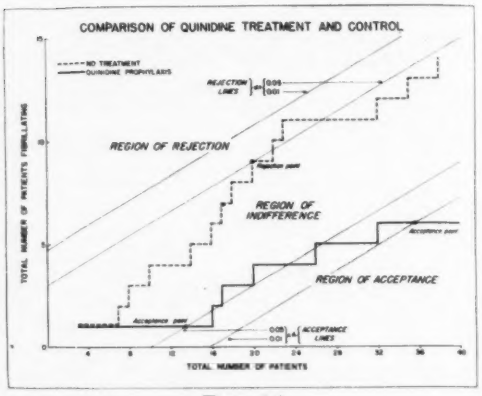

Figure 1

Sequential probability ratio test of the hypothesis that with quinidine prophylaxis the number of patients developing atrial fibrillation after mitral valvuloplasty is less than 20 per cent. The sequential curve for the control group (no quinidine) is seen to cross the rejection line after 20 cases with a probability of error of 5 per cent. The curve for quinidine treatment crosses into the acceptance region (probability 5 per cent) after 14 cases. It also crosses the stricter 1 per cent line after 36 cases.

Prospective Study

In the prospective study sequential analysis was employed to test the significance of results in the 41 pairs of patients in group III. This method provides an effective and economical statistical design for clinical experiments.[16–18] In this test independent evaluations of effectiveness of the two treatments (quinidine and control) were made. Guided by the results in the retrospective study the test was set up so that the treatment would be judged acceptable if it resulted in fewer than 20 per cent failures, whereas it would be rejected if it led to more than 40 per cent

Table 2

Influence of Various Clinical Factors on Incidence of Postoperative Atrial Fibrillation Group III—Combined Series

Clinical factor	Quinidine			Control		
	AF/total	%AF	Chi-square	AF/total	%AF	Chi-square
Prior AF, APB*						
or palpitation	5/11	46		7/13	54	
None	4/30	13	4.85‡	7/28	25	3.28
Arthralgia	1/6	17		4/9	45	
None	8/35	23	0.12	10/32	31	0.55
Associated MI†	21/95	22		18/40	45	
None	31/132	23	0.07	11/34	32	0.5
Aschoff bodies	25/108	23		11/34	32	
None	24/111	22	——	20/42	48	1.86
Male	19/47	40		10/16	63	
Female	32/183	18	11.41§	22/61	36	3.64
Male above 35	19/40	48		5/8	63	
Male under 35	0/7	0	5.48‡	5/8	63	——
Female above 35	20/98	20		13/30	43	
Female under 35	12/85	14	1.12	9/31	29	1.35

*Atrial premature beats.
†Mitral Insufficiency.
‡p less than 0.05
§p less than 0.001

failures. In figure 1 the limits of 5 and 1 per cent error are shown. Separate curves for quinidine and control groups were drawn with the number of patients who fibrillated plotted against the total number of observations. The first time that either sequential curve crosses into the acceptance or rejection region, the appropriate decision is made.

In figure 1 it can be seen that the quinidine prophylaxis method was found acceptable at the lower 5 per cent level after only 14 cases and at the stricter 1 per cent level after 36 cases. On the other hand, the control method was found unsatisfactory after 20 cases at the 5 per cent level. Continuation of the test did not lead to rejection at the 1 per cent level by the forty-first case. Testing would have to be carried further to check the stronger criterion. These tests established that quinidine prophylaxis significantly decreased the incidence of postoperative atrial fibrillation.

As a further check on the validity of this conclusion these data were subjected to a runs analysis[19] to test the randomness of each group individually. It was found that: 1. In the control group the series could represent a random series of trials. 2. In the quinidine-treated group with a level of confidence much greater than 99 per cent, it can be said that the sequence of values is not random, indicating the establishment of a definite trend. This finding may be taken as further evidence of the validity of the quinidine effect.

Analysis of the Combined Series

Since in the retrospective and prospective studies the incidence of atrial fibrillation in the control and treated groups was virtually the same, the two series were combined in order to provide additional clinical information. There were 308 group-III patients in the combined series. Of this number 229 received quinidine and 50 or 22 per cent developed atrial fibrillation, while of 79 patients who did not receive this medication 33 or 42 per cent fibrillated. The Chi-square test indicated that the difference is statistically significant (p is less than 0.001). In 39 group-IV patients, however, the administration of quinidine prophylactically resulted in a reduction of postoperative atrial fibrillation

Table 3

Prediction of Results with and without Quinidine Phophylaxis in Group-III Patients with Normal Sinus Rhythm Undergoing Mitral Valve Operation. (An Example)

	No quinidine	Quinidine treated
Number of patients	100	100
Postoperative atrial fibrillation	42	22
Spontaneous reversion to normal sinus rhythm	10	8
Conversion with quinidine	25	12
Remaining in atrial fibrillation	7	2

from 62 per cent in controls to only 50 per cent in those treated. This difference is not statistically significant (p greater than 0.05).

In both the quinidine and the control series the median day of onset of atrial fibrillation was the third postoperative day. There appears to be a tendency for a greater number of those who received quinidine to develop the arrhythmia after the ninth day. There is no significant difference, however, in the mean days of onset between the two series (p equals 0.18).

In 27 patients of the prospective series a quinidine blood level was obtained on the first postoperative day 2 hours following one of the four doses. There is almost no difference between the levels observed for those who remaind in normal sinus rhythm (mean 4.44 mg./L.) and those who fibrillated (mean 4.7 mg./L.). Although considerable scatter is present in both groups, those who developed atrial fibrillation had a mean quinidine blood level that was actually higher (mean 5.9 mg./L.; range 4.3 to 9.8) than the mean of the value obtained on the seventh postoperative day in those patients who remained in normal sinus rhythm (mean 4.04 mg./L.; range 1.9 to 8.0).

The influence of various clinical factors on the incidence of postoperative atrial fibrillation was also examined in this combined series. Table 2 presents the results of this analysis. In the control patients, receiving no quinidine, arthralgia as an indicator of rheumatic activity, the presence of mitral insufficiency and age beyond 35 years did not significantly alter the incidence of this arrhythmia. In these patients, however, the occurrence of prior atrial fibrillation, episodes of palpitation, and male sex resulted in approximately a two-fold increase in percentage of fibrillation. These differences, however, were just short of significance at the 5 per cent confidence level by Chi-square test.

These factors, namely, prior atrial arrhythmia, palpitation, and male sex were associated with an increased incidence of postoperative atrial fibrillation even when the patients were receiving prophylactic quinidine. Of the men who received quinidine, those above 35 years of age had a significantly greater incidence of this arrhythmia. It is noteworthy that the same factors (prior arrhythmia and male sex) caused a distinct increase in incidence of postoperative fibrillation in both control and treated groups. The failure to achieve the 5 per cent confidence level in the controls may be due to the small number of observations available for analysis.

Unlike atrial fibrillation occurring in the course of untreated mitral stenosis, the postoperative arrhythmia frequently reverted spontaneously without specific treatment other than rate control with increased doses of digitalis. Thus in group III, of 82 patients who fibrillated postoperatively, 27 or 33 per cent reverted spontaneously to normal sinus rhythm. In group IV 5 of 22 or 23 per cent reverted. There was no significant difference between the rates of spontaneous reversion whether or not quinidine prophylaxis had been employed.

In the majority of those patients who remained in atrial fibrillation even though the ventricular rate was controlled with digitalis, an attempt was made to revert the arrhythmia with quinidine on about the tenth postoperative day by the method of Sokolow.[20] In group III this was successful in 89 per cent of trials and in group IV in 86 per cent.

Discussion

Atrial fibrillation is a common occurrence after pulmonary operations.[21, 22] The reported

incidence after pneumonectomy is 45 per cent when the resection is carried out within the pericardium and 21 per cent when the pericardium is not entered.[22] This incidence can be reduced by the prophylactic administration of quinidine to 14 and 9 per cent respectively.[22] Similar good results from prophylactic quinidine have been noted after mitral valvuloplasty. Kittle and Crockett[3] found that the incidence of the arrhythmia was lowered from 32 to 15 per cent when quinidine and digitalis were employed together. Other observers, however, with extensive experience with patients undergoing mitral valvular surgery have reported no benefit from the use of quinidine.[2, 5] To date there has been no deliberate, objective study of the value of quinidine that has employed adequate controls and randomized treatment to minimize observer bias.

The present study conclusively demonstrates the value of quinidine in preventing atrial fibrillation after mitral valvuloplasty. From these results one would predict that in 100 patients of group III with normal sinus rhythm undergoing mitral valvuloplasty the use of quinidine will reduce the number who fibrillate postoperatively from 42 to 22. Eight of the 22 who thus fibrillate will revert spontaneously to normal sinus rhythm when their rate is controlled with additional doses of digitalis. Normal rhythm can be restored in 12 of the remaining 14 patients by the use of quinidine in increasing doses after the tenth postoperative day. Two patients of the original 100 will remain permanently in atrial fibrillation. When, however, prophylactic quinidine is not employed seven patients will remain in this disordered rhythm (table 3).

On the matter of dosage of quinidine to be used prophylactically, Kittle and Crockett advocate 0.4 Gm. every 4 hours or 2.4 Gm. per day.[3] They note that their program requires daily monitoring of the electrocardiogram and serum quinidine levels. No convincing evidence is provided that this high dose is of any greater benefit than a lesser amount. Indeed our analysis of two dosage regimens (0.8 and 1.2 Gm. per day) indicates that the smaller amount gives equally good results.

In our series with total daily doses of 0.8 to 1.2 Gm. per day there were no deaths and no quinidine-induced arrhythmias. Quinidine had to be discontinued in only two patients of the 82 in the prospective study at 4 and 9 days postoperatively, respectively, because of gastrointestinal intolerance.

Conclusions

A study has been conducted to determine the effectiveness of quinidine prophylaxis in reducing the incidence of atrial fibrillation in patients with normal sinus rhythm undergoing operation for mitral stenosis. In both a retrospective study of 226 group-III patients and in a more rigidly controlled prospective study of 41 pairs of patients a statistically significant reduction in the incidence of this arrhythmia was observed (from 42 to 22 per cent). Moderate dosages (0.8 to 1.2 Gm. per day) were effective.

A history of palpitation or prior episodes of atrial fibrillation and male sex appeared to be related to the development of postoperative atrial fibrillation. Associated mitral insufficiency, Aschoff bodies in the atrial appendage, and recent history of arthralgia did not appear to increase significantly the incidence of this arrhythmia.

If prophylactic quinidine is employed and reversion is attempted after the tenth postoperative day in those patients who nonetheless developed atrial fibrillation, only 1.5 per cent of patients in normal sinus rhythm operated on for mitral stenosis will be discharged from the hospital with an irregular rhythm.

References

1. Ellis, L. B., Harken, D. E., and Black, H.: A clinical study of 1,000 consecutive cases of mitral stenosis two to nine years after mitral valvuloplasty. Circulation 19: 803, 1959.
2. Wood, P.: An appreciation of mitral stenosis: Clinical features, investigations and results. Brit. M. J. 1: 113, 1954.
3. Kittle, C. F., and Crockett, J. E.: The etiology and prevention of atrial fibrillation after mitral valvotomy. J. Thor. & Cardiov. Surg. 38: 353, 1959.
4. Dimond, E. G., and dos Santos, E. M.: Com-

plications following mitral commissurotomy with special reference to auricular fibrillation. J. Kansas M. Society 55: 120, 1954.

5. Goodwin, J. F., Hunter, J. D., Cleland, W. P., Davies, L. G., and Steiner, R. E.: Mitral valve disease and mitral valvotomy. Brit. M. J. 2: 573, 1955.
6. Heinz, R., and Hultgren, H.: Atrial fibrillation following mitral valvotomy. Arch. Int. Med. 99: 896, 1957.
7. Hansen, W. R., McClendon, R. L., and Kinsman, J. M.: Auricular fibrillation: Hemodynamic studies before and after conversion with quinidine. Am. Heart J. 44: 499, 1952.
8. Hecht, H. H., Osher, W. J., and Samuels, A. J.: Cardiovascular adjustments in subjects with organic heart disease before and after conversion of atrial fibrillation to normal sinus rhythm. J. Clin. Invest. 30: 647, 1951.
9. Kerkof, A. C.: Minute volume determinations in mitral stenosis during auricular fibrillation and after restoration of normal rhythm. Am. Heart J. 11: 206, 1936.
10. Kory, R. C., and McNeely, G. R.: Cardiac output in auricular fibrillation with observation on the effects of conversion to normal sinus rhythm. J. Clin. Invest. 30: 653, 1951.
11. Donald, W. K.: Pulmonary vascular resistance in mitral vascular disease. *In* Pulmonary Circulation. Edited by Wright R. Adams and Ilza Veith. New York, Grune & Stratton, Inc., 1959, p. 285.
12. Seltzer, A.: Effect of atrial fibrillation upon the circulation in patients with mitral stenosis. Am. Heart J. 59: 518, 1960.
13. Bryfogle, J. W., Santilli, T., Saltzman, H. A., and Bellet, S.: Therapeutic and toxic indices of digitalis: A comparative study of gitalin and digitalis leaf. New England J. Med. 256: 767, 1957.
14. Daley, R., McMillan, I. K. R., and Gorlin, R.: Mitral incompetence in experimental auricular fibrillation. Lancet 2: 18, 1955.
15. Corday, E., Gold, H., deVera, L. B., Williams, J. H., and Fields, J.: Effect of the cardiac arrhythmias on the coronary and systemic circulations. Ann. Int. Med. 50: 535, 1959.
16. Wald, A.: Sequential Analysis. New York, John Wiley & Sons, 1952.
17. Bartholomay, A. F.: The sequential probability ratio test applied to the design of clinical experiments. New England J. Med. 256: 498, 1957.
18. Cass, L. J., Frederick, W. S., and Bartholomay, A. F.: Methods of evaluating ethoheptazine and ethoheptazine combined with aspirin. J.A.M.A. 166: 1829, 1958.
19. Siegel, S.: Non-Parametric Statistics for the Behavioral Sciences. New York, McGraw-Hill Book Company, Inc., 1956.
20. Sokolow, M.: The present status of therapy of the cardiac arrhythmia with quinidine. Am. Heart J. 42: 771, 1951.
21. Cerney, C. I.: The prophylaxis of cardiac arrhythmias complicating pulmonary surgery. J. Thoracic Surg. 34: 105, 1957.
22. Hurt, R. L., and Bates, M.: The value of quinidine in the prevention of cardiac arrhythmias after pulmonary resection. Thorax 13: 39, 1958.

A single well-applied fact may carry conviction where reasoning will not.—Dominic John Corrigan, M.D. *The Lancet* 1: 586, 1829.

Long-Term Results of Aortic-Pulmonary Anastomosis for Tetralogy of Fallot

An Analysis of the First 100 Cases Eleven to Thirteen Years after Operation

By MILTON H. PAUL, M.D., ROBERT A. MILLER, M.D., AND WILLIS J. POTTS, M.D.

THE CLASSICAL subclavian-pulmonary[1] and aortic-pulmonary[2] anastomoses were devised as palliative surgical maneuvers for the tetralogy of Fallot complex to augment pulmonary blood flow and to increase systemic arterial saturation. These shunt procedures, performed during the past 14 years, have provided reasonably good health to thousands of patients with severe cyanosis and physical limitation.

More recently, intracardiac surgical technics supported by an extracorporeal pump-oxygenator circulation have provided a "corrective" repair for this lesion. Although a moderately high initial surgical mortality has persisted in many clinics, it seems apparent that this form of open intracardiac repair will become the treatment of choice in suitably selected patients.

The present report is concerned with the long-term results of one form of shunt procedure, the aortic-pulmonary anastomosis, as a surgical therapy for tetralogy of Fallot.

Clinical Material

Our study is concerned with the first 100 consecutive patients with a diagnosis of tetralogy of Fallot upon whom an aortic-pulmonary anastomosis could be performed. The diagnostic term, tetralogy of Fallot, cannot be too rigidly interpreted in respect to this group of patients, since the diagnosis at this early period (1946-1948) of our congenital heart surgery program was completely without assistance from angiocardiography or catheterization.

This initial group of patients, operated upon at The Children's Memorial Hospital in 1946-1948, was comprised in general of (a) older children in rather desperate condition who had somehow remained alive, and (b) a considerable number of infants and smaller children for whom aortic-pulmonary anastomosis was especially devised. Eleven patients were below 12 months of age, 29 patients between 12 and 36 months, 32 patients between 3 and 6 years of age, and 28 over 6 years of age. Severe cyanosis, extreme limitation in locomotion, and frequent squatting were the rule rather than the exception.

Persistence and good fortune have enabled us to obtain follow-up information in 1959 on 92 of the first 100 consecutive patients operated on in 1946-1947 (table 1). Three fourths of the surviving patients have had clinical, electrocardiographic, and x-ray evaluations in our own clinic. The others were evaluated on the basis of telephone interviews as well as written questionnaires and, whenever possible, recent chest x-rays, and reports of physical examination were provided by the family physician.

Operation

An aortic-pulmonary anastomosis was performed in each of these 100 patients as the initial surgical therapy.

The size of the anastomotic channel was carefully planned by the use of calipers to measure the length of the incisions in the aorta and pulmonary artery. At first, these incisions were made 8 mm. long and this provided an anastomotic channel 5 mm. in diameter. Marked postoperative enlargement in the heart of the fourth patient in this series (J. P. fig. 1) prompted shortening these incisions to 6.3 mm., which produced a channel diameter of 4 mm. We have continued to make the incision 6.3 mm. long in all children except infants, in whom they are made 5 mm. long, since in some instances considerable growth of the anastomotic channel can be anticipated.[3]

To our knowledge, only three patients in this group have required a second operation to relieve recurrent cyanosis. The clinical

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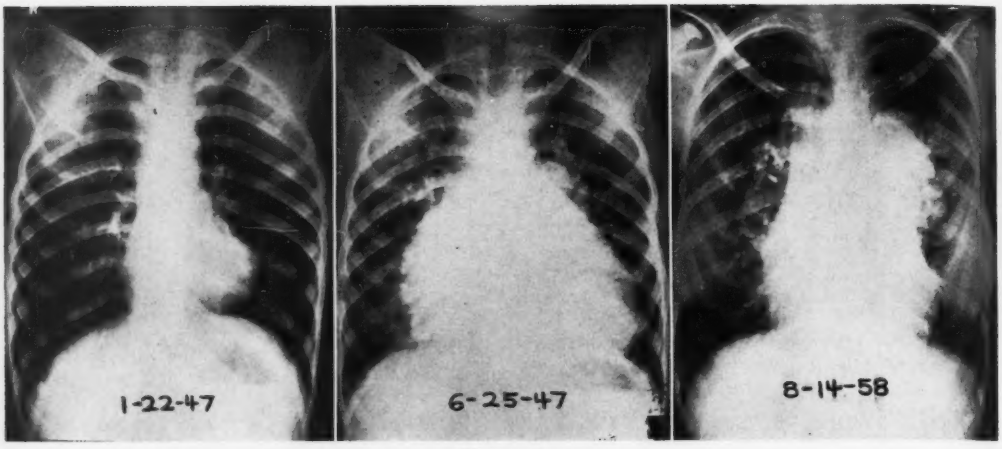
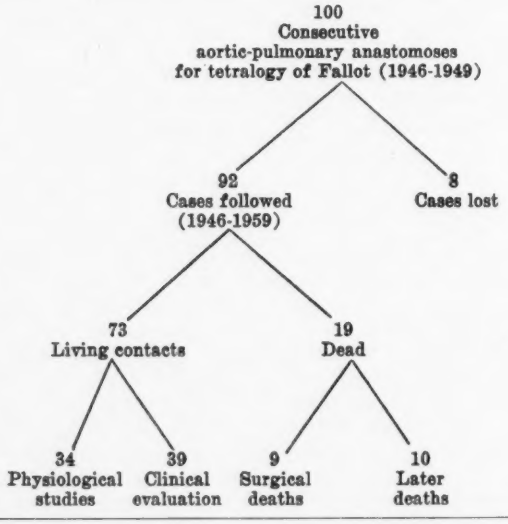


Figure 1

Marked cardiac enlargement and congestive heart failure following surgical anastomosis with long-term poor (group III) clinical result and severe pulmonary artery hypertension. Preoperative (1-22-47), early postoperative (6-25-47), and long-term follow-up (8-14-58) x-rays.

Table 1

Analysis of the First 100 Consecutive Patients with a Diagnosis of Tetralogy of Fallot upon Whom an Aortic-Pulmonary Anastomosis Could Be Performed



details are presented in an earlier follow-up report.[4] It should be noted here, however, that in two of these three cases the aortic-pulmonary anastomosis was performed on the right side in the presence of a right aortic arch, a procedure long abandoned because of technical difficulties.

Mortality

Ninety-two of the first 100 patients are accounted for in table 1 and of this number

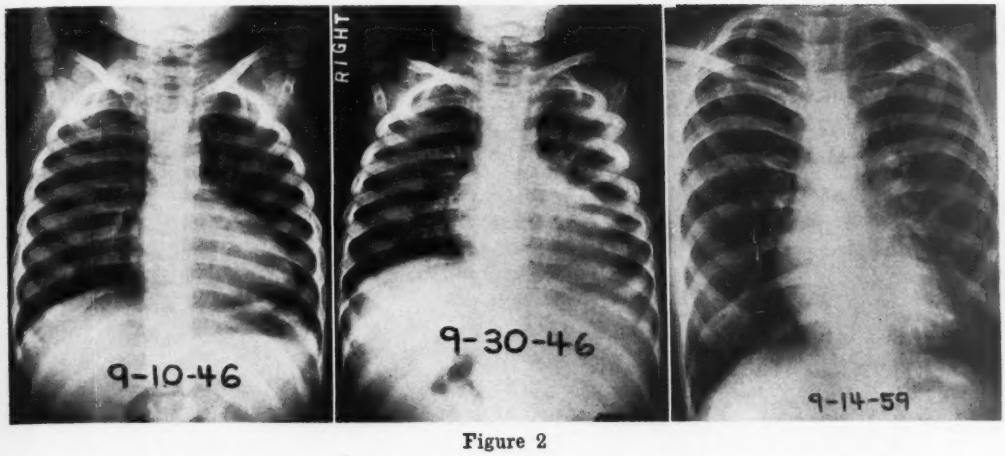


Figure 2

Normal heart size and excellent (group IA) clinical result 13 years after aortic-pulmonary anastomosis surgery. Preoperative (9-10-46), and long-term follow-up (9-14-59) x-rays.

19 are known to be dead. Nine of the 100 patients subjected to an aortic-pulmonary anastomosis in this early period (1946-1948) died at operation or in the immediate postoperative period.

The over-all operative mortality through the years for this surgical procedure in approximately 700 patients has been 9 per cent. In patients under 3 years of age the operative mortality has persistently averaged 12 to 15 per cent, and in patients over 3 years of age it has been 3.8 to 4.0 per cent.

After leaving the hospital improved by surgery an additional 10 patients are known to have died in the period from 1946 to 1959. Table 2 briefly indicates the known causes of death in this group and the interval between surgery and death.

Clinical Evaluation

Our major interest in this study was to determine the clinical results in those 73 patients known to be alive 11 to 13 years after an aortic-pulmonary anastomosis was performed for tetralogy of Fallot. The evaluation of the postoperative status presented in table 3 is primarily based upon criteria suggested by Potts et al.[4] and Taussig and Bauersfeld.[5] These criteria are obviously not an accurate measure of the cardiovascular status of a given individual, since they are based solely upon the degree of relief of cyanosis and a subjective evaluation of general clinical improvement and increased exercise tolerance. Such important factors as the presence of marked cardiac enlargement, severe pulmonary hypertension, and aneurysmal dilatation of the pulmonary arteries are not taken into consideration. This evaluation, however, does represent the past and present status of the patient with regard to his ability to carry out day-to-day normal activities.

Group I patients are those who show little or no cyanosis at rest and slight cyanosis during exercise. They are able to attend public school, college, or work, and in general do what other children or young adults do with the exception of the more violent forms of activity. Many, however, will admit under careful questioning that they tire more easily than their schoolmates or friends. In this present report we have separated from group I, a IA group, which represents those individuals who can carry out rather extreme activity with what appears to be a normal degree of fatigue. These activities include manual farming, ballet dancing, skiing, and long-distance bicycling.

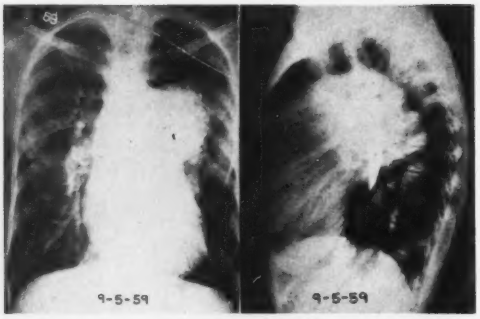


Figure 3

Pulmonary artery aneurysm (A-P and lateral chest x-rays).

It seems appropriate, although somewhat repetitious, to review briefly the clinical course of the first patient upon whom an aortic-pulmonary anastomosis was performed.

Diane S., age 21 months, weighing 18 lbs., was admitted to The Children's Memorial Hospital September 9, 1946. She was deeply cyanotic, unable to stand, and, following the slightest exertion, even too rapid eating, became unconscious. Her red blood cell count was 10,300,000 per mm.[3] Clinical and laboratory data confirmed the diagnosis of tetralogy of Fallot.

On Friday September 13, 1946, an aortic-pulmonary anastomosis was performed. The anastomotic channel theoretically was made 5 mm. in diameter, but actually must have been considerably smaller. During the first operation of this kind anxiety about possible hemorrhage or later leakage undoubtedly led to too snug sutures and to irregular placement of sutures.

She had a surprisingly uneventful postoperative recovery. Within a few months she gained considerable weight and learned to walk. Needless to say, this patient has been followed most intently during the past 13 years.

In figure 2 are shown roentgenograms of her heart immediately before operation, two weeks later, and 13 years after operation. A rather high pitched, continuous murmur has persisted unchanged throughout these years. This child, now a bright-eyed, attractive, 15-year-old girl, engages in all the regular and irregular activities common to this age group. During the summer of 1959, with one of her unhandicapped friends, she bicycled 30 miles in 1 day. Parental displeasure with this unauthorized escapade did not seem to lessen her pleasure in being able to demonstrate to herself and to her parents that she was capable of such strenuous activity. It is unfortunate that all patients subjected to shunt procedures cannot have equally good results.

Table 2

Cause of "Late Deaths" Following Aortic-Pulmonary Anastomosis for Tetralogy of Fallot

Patient no.	Cause of death	Interval after surgery
54	Brain abscess	3 mo.
15	(?)	2 yr.
20	Lobar pneumonia	2 yr.
36	Congestive heart failure	2 yr.
76	Congestive heart failure	2 yr.
26	Congestive heart failure	7 yr.
95	Congestive heart failure	8 yr.
3	Congestive heart failure	13 yr.
4	Subacute bacterial endocarditis	13 yr.
33	(?) Sudden death	13 yr.

Group-II patients may tire easily on moderate exercise. All show moderate to marked improvement over their condition before surgery; however, some have persistent, mild cyanosis at rest, and all have definite decreased exercise tolerance. In group III are classed those patients who are unable to perform normal daily activities without considerable fatigue.

Eleven to 13 years following the aortic-pulmonary anastomosis surgery two thirds of the patients can be classified (table 3) as having good or moderately good results (group IA, I). The earlier clinical evaluation (1954) gave a somewhat higher percentage of good results. Approximately one third of the patients are classified now as group II, fair results. In the poor-result group III are two patients: one who has severe pulmonary hypertension and pulmonary vascular obstruction and one who still has an inadequate pulmonary blood flow despite a second shunt procedure.

Roentgenographic Findings

Recent roentgenograms of the chest were available in 58 of the 73 contacted, living patients and cardiac enlargement was evaluated both by cardiothoracic ratio measure-

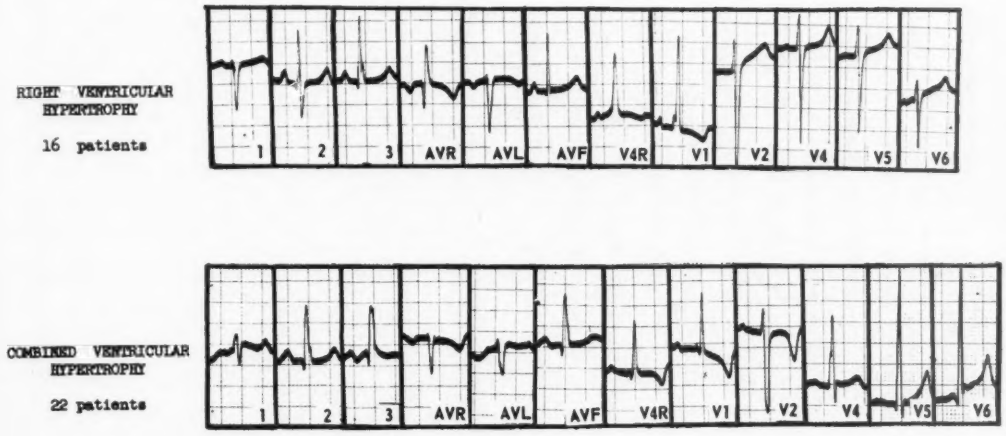


Figure 4

Electrocardiographic evaluation in 45 patients with tetralogy of Fallot 11 to 13 years after aortic-pulmonary anastomosis.

Table 3

Clinical Evaluation in "Tetralogy of Fallot" Eleven to Thirteen Years after Aortic-Pulmonary Anastomosis

			1959 (73 Patients)	1959 (73 Patients)	1954 (86 Patients)
Group	IA	Excellent	7	10%	——
Group	I	Good	42	58%	79%
Group	II	Fair	22	30%	19%
Group	III	Poor	2	2%	2%

Table 4

X-ray Evaluation in Tetralogy of Fallot Eleven to Thirteen Years after Aortic-Pulmonary Anastomosis (Fifty-Eight Patients)

Cardiac size	Patients	Pulmonary artery size	Patients
Normal	5	Normal or	
Slight enlargement	17	slight enlargement	14
1+	28	1+	22
2+	8	2+	17
3+	0	3+	5

Table 5

Cardiac Catheterization Findings in Tetralogy of Fallot Eleven to Thirteen Years after Aortic-Pulmonary Anastomosis (Eighteen Patients)

Pulmonary pressure Mm. Hg (mean)	Patients	Pulmonary flow L./min./M.^{2}	Patients	Pulmonary resistance Units	Patients
<20	10	4—6	8	<3	15
20—30	5	6—8	3	3—5	1
30—50	3	8—14	7	>5	2

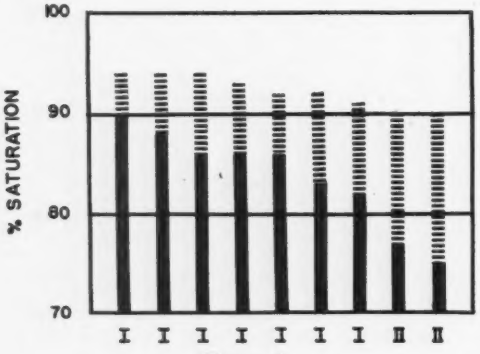


Figure 5

Systemic arterial oxygen saturation response to mild exercise.

ments and clinical estimate (table 4). The majority of the patients had a slight to moderate cardiac enlargement after more than 10 years of a functioning aortic-pulmonary anastomosis. There were five patients with normal heart size (fig. 2), and none was found living at present with extreme cardiac enlargement.

Slight cardiac enlargement is anticipated in the early postoperative period if satisfactory clinical improvement is to occur. Although the heart size following any cardiac operation is undoubtedly an important factor in prognosis, there was not always a good correlation in this group with the clinical, symptomatic evaluation. One half of the patients with moderate (2+) cardiac enlargement had a good (group I, IA), long-term clinical result.

Dilatation and progressive enlargement of the main pulmonary artery branches were not uncommon and, if extreme, (fig. 3) represented a problem at the time of corrective surgery. Twenty-two patients demonstrated a considerable degree of pulmonary artery dilatation (2+, 3+).

Electrocardiographic Findings

In figure 4 the present electrocardiographic status in 45 patients is summarized. Although preoperative electrocardiograms with complete precordial chest leads are not available from the 1946-1948 period, it is reasonable to assume that almost all of these patients had

Table 6

Systemic Arterial Oxygen Saturation at Rest Eleven to Thirteen Years after Aortic-Pulmonary Anastomosis

% Saturation	Patients
91—94	12
86—90	8
81—85	4
<80	3

the typical right ventricular hypertrophy pattern of tetralogy of Fallot.

One third of the patients studied have maintained this typical right ventricular hypertrophy pattern with tall R waves in the right precordial leads and deep reciprocal S waves over the left precordium. Combined ventricular hypertrophy is now present in two thirds of the patients, indicating that there has been a considerable increase in left ventricular work following the surgical anastomosis with its attendant increase in pulmonary blood flow. This is well illustrated in the lower electrocardiogram, which has tall R waves in the right precordial leads, V_{4R} and V_1, and also extremely tall, R waves in the left precordial leads, V_5 and V_6.

Physiologic Studies

A small, unselected group of 27 patients were studied by right heart catheterization. The pulmonary artery was entered in 18 patients, and the aorta in 21 patients. Since we were particularly interested in an assessment of the pulmonary pressure, blood flow, and vascular resistance, the data obtained in these 18 patients are summarized in table 5. The difficulty of obtaining adequate, representative blood sampling from the pulmonary artery in the presence of a large aortic-pulmonary anastomosis must be considered in evaluating some of the measurements of pulmonary blood flow and pulmonary vascular resistance. The majority of the pulmonary artery blood samples were obtained, however, from the nonanastomosed pulmonary artery branch.

After 11 to 13 years of a functioning aortic pulmonary anastomosis 10 patients had pulmonary artery mean pressures of less than

20 mm. Hg and only three patients had grossly elevated mean pressures (45, 75, 85 mm. Hg). The pulmonary blood flow estimates indicate the wide range (4 to 14 L./min./M.^{2}) present in these 18 patients. Finally there were 15 patients with normal pulmonary vascular resistance and three patients with estimated resistances (5.0, 15.8, and 18.0 units) greater than the normal level of approximately 3 units.

Table 6 illustrates that almost one half of this group had a resting arterial oxygen saturation at or above 90 per cent. The effect of mild exercise (3 minutes of continuous bicycling movements of the legs) in nine patients with resting arterial oxygen saturations above 90 per cent is illustrated in figure 5. The first seven patients were all classified in clinical group I (good) and all demonstrated a fall in oxygen saturation into the 80 to 90 per cent saturation range. The last two patients were in clinical group II (fair) and both demonstrated a more pronounced fall.

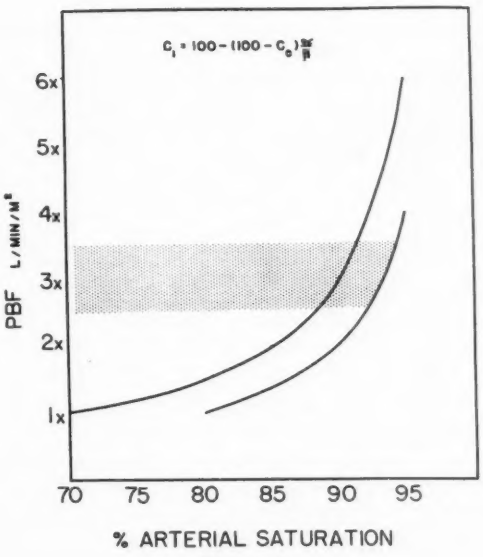


Figure 6

Relationship of postoperative arterial oxygen saturation to the increased pulmonary blood flow resulting from surgical aortic-pulmonary anastomosis.

Discussion

The present long-term (11-13 year) follow-up study reinforces the findings presented in an earlier (6-8 year) report on the first 100 consecutive patients operated upon at The Children's Memorial Hospital for tetralogy of Fallot during 1946-1948. The data concerning operative mortality, over-all mortality, and incidence of good results from several other large, but not homogeneous series[6, 7] are in approximate agreement with our figures of 9, 19, and 70 per cent for these three categories.

Although it has become quite clear that open-heart resection of the infundibular obstruction and closure of the interventricular septal defect is the ideal procedure for tetralogy of Fallot, it seems equally clear, at this time, that an anastomotic operation remains the procedure of choice for the severely cyanotic infant, perhaps under the age of 2 or 3 years, who is subject to repeated syncopal attacks and needs immediate surgical relief. In this severely cyanotic young group, are the patients who present an unusually high surgical risk from open-heart corrective surgery. As yet undefined factors, such as marked aortic overriding, a small left ventricular chamber, and certainly pulmonary hypoplasia bordering on atresia, contribute to reported mortalities of about 50 per cent in this age group. Age-dependent difficulties are also reflected in the mortality statistics on shunt procedures, with the mortality ranging from 9 to 17 per cent below 3 years of age as opposed to 2.5 to 4.5 per cent in older patients.[7] The long-term clinical results appear to be less age-dependent than the mortality rate; nevertheless, a higher percentage of good results was obtained in patients over 6 years of age (table 7).

A review of the long-term clinical course of these patients indicates that a considerable degree of stabilization resulted 1 to 2 years after the aortic-pulmonary anastomosis had been performed. It further appears that the long-term poor results were most likely related to the presence of too large an anastomosis, leading either to left ventricular over-

Table 7

Relationship of Age at Time of Surgery to Long-Term Clinical Results

Age at operation	Group IA + I No. patients	Group II + III No. patients
<3 yr.	17	10
3—6 yr.	18	9
>6 yr.	14	5

work and congestive heart failure or to severe pulmonary hypertension and probably progressive pulmonary vascular obstruction and a decreasing aortic-pulmonary shunt. A counterpart to these clinical implications of too large an anastomosis may be found in the experimental results of Heath et al.,[8] who found severe pulmonary vascular pathologic changes analogous to hypertensive pulmonary vascular disease in a dog who had an aortic-pulmonary anastomosis for nearly 4 years before necropsy.

Since it seems likely that the aortic-pulmonary anastomosis will, at least for the present, continue to serve as a valuable salvage operation for a small segment of patients with tetralogy of Fallot and for certain other complex cyanotic lesions (pulmonary atresia, tricuspid atresia, transposition of the great vessels with severe pulmonary stenosis), some further discussion is directed toward the factors leading to difficulties.

The critical size of an aortic-pulmonary anastomosis for optimum relief of cyanosis requires meticulous surgical technic. Even if the initial anastomotic channel is of ideal size, there remains the problem of growth of the anastomosis with the passage of time. Some preliminary experimental studies[3] performed on rapidly growing pigs indicate that progressive enlargement of the anastomosis does occur; however, about half of the animals showed no growth in the orifice size.

It must further be observed that improvement in the arterial oxygen saturation above a conservative level is purchased only at the cost of a markedly increased pulmonary blood flow, an obviously large aortic-pulmonary anastomosis, and a markedly increased left ventricular work load. Born et al.[9] have shown that, assuming a relatively constant oxygen consumption before and after operation, the resultant arterial oxygen saturation (C_1) is dependent upon the preoperative arterial oxygen saturation (C_0) and the increase in pulmonary blood flow $\frac{\alpha}{\beta}$ that surgery has provided. In figure 6 the curved line indicates that a preoperative arterial saturation of 70 per cent would be increased to approximately 87 to 90 per cent if the pulmonary blood flow were increased approximately threefold. The steeply ascending slope of the pulmonary blood flow curve in the region of 90 per cent arterial oxygen saturation indicates that any further significant increase in arterial saturation to the point of abolishing clinical cyanosis is derived from a markedly increased pulmonary blood flow and left ventricular work load.

In reviewing the long-term clinical results of the aortic-pulmonary anastomosis for tetralogy of Fallot it is important to consider the problems to be anticipated when corrective open-heart surgical repair is undertaken in such patients. At the present time the technical problems of isolating and "taking down" a large, functioning aortic-pulmonary anastomosis are considerably greater than those of a subclavian-pulmonary anastomosis. In two patients from our 1946-1948 group open-heart "corrective" surgery has been performed with good clinical results. Continuing experience with this reoperation problem, however, has indicated a high operative morbidity and mortality. Thus, in circumstances in which early shunt surgery is indicated and future open-heart surgery is anticipated, the subclavian-pulmonary anastomosis, if surgically possible, may be the preferable procedure.

Summary

The first 100 consecutive patients with a diagnosis of tetralogy of Fallot upon whom an aortic-pulmonary anastomosis could be performed were subjected to a clinical and physiologic evaluation 11 to 13 years after operation.

At this long-term follow-up 92 patients were traced. Nine patients died at the time of surgery and, in the period from 1946 to 1959, 10 patients died, most often from congestive heart failure. To our knowledge only three patients have required a second shunt operation to relieve recurrent cyanosis. The clinical results were considered good or excellent in 68 per cent of the survivors, fair in 30 per cent, and poor in 2 per cent.

The long-term poor results and mortality were usually associated with too large an initial anastomosis leading to either left ventricular overwork and congestive heart failure or severe pulmonary hypertension and progressive pulmonary vascular obstruction.

Right heart catheterization studies indicated that in a group of 18 patients in whom the pulmonary vascular bed could be evaluated, 15 patients had a normal pulmonary vascular resistance after 11 to 13 years of a clinically adequate aortic-pulmonary shunt.

The role of the shunt procedures as a valuable salvage operation at the present time for a select segment of patients with tetralogy of Fallot and certain other complex cyanotic lesions is reemphasized.

References

1. Balaock, A., and Taussig, H. B.: Surgical treatment of malformations of the heart in which there is pulmonray stenosis or pulmonary atresia. J.A.M.A. **128**: 189, 1945.
2. Potts, W. J., Smith, S., and Gibson, S.: Anastomosis of aorta to pulmonary artery: Certain types in congenital heart disease. J.A.M.A. **132**: 627, 1946.
3. Potts, W. J., and Riker, W. L.: Study of growth of aortic-pulmonary anastomoses. Surg., Gynec. & Obst. **94**: 358, 1952.
4. Potts, W. J., Gibson, S., Berman, E., White, H., and Miller, R. A.: Surgical correction of tetralogy of Fallot. J.A.M.A. **159**: 95, 1955.
5. Taussig, H. B., and Bauersfeld, S. R.: Follow-up studies on the first 1000 patients operated on for pulmonary stenosis or atresia. Ann. Int. Med. **38**: 1, 1953.
6. Campbell, M.: Late results of operations for Fallot's tetralogy. Brit. M. J. **2**: 1175, 1958.
7. Shumacker, H. B., Jr., and Mandelbaum, I.: Results of shunt procedures in tetralogy of Fallot. Surgery **47**: 320, 1960.
8. Heath, D., Donald, D. E., and Edwards, J. E.: Pulmonary vascular changes in a dog after aortic-pulmonary anastomosis for four years. Brit. Heart J. **21**: 187, 1959.
9. Born, G. V. R., Dawes, G. S., Mott, C., and Rennick, B. R.: The relief of central cyanosis caused by pulmonary arteriovenous shunts by construction of an artificial ductus arteriosus. J. Physiol. **130**: 167, 1955.

In the physician or surgeon no quality takes rank with imperturbability.—Sir William Osler. *Aphorisms From His Bedside Teachings and Writings.* New York, Henry Schuman, Inc., 1950, p. 85.

Clinical Evaluation of Intravenous Abdominal Aortography and Peripheral Arteriography

By ISRAEL STEINBERG, M.D.

THE ROBB-STEINBERG method of visualization of the cardiovascular system by the rapid intravenous injection of concentrated organic iodides and precise roentgenography has been available since 1938.[1-3] Recently, modification of the method by the rapid, simultaneous, and bilateral injection of concentrated contrast media after accurate prediction of the circulation time has achieved abdominal aortography, peripheral arteriography, and cerebral angiography.[4-5] Inexpensive needle stop-cock units, 12-gage syringes, and the use of roentgen equipment ordinarily on hand for gastrointestinal or genitourinary roentgenography make this method readily available and practical for use in the average well-equipped radiologic department.

Almost 300 patients have had abdominal aortography and peripheral arteriography with the intravenous method. The purpose of this report is to reiterate the principles and emphasize the details of the method of intravenous abdominal aortography and peripheral arteriography and to discuss and illustrate its value for diagnosis of disease of the abdominal aorta and its branches.

Method

The intravenous method of abdominal aortography and peripheral arteriography[5] depends upon the principles developed for angiocardiography.[1-8] Speed of injection of the contrast material is essential and this is accomplished by simultaneously injecting the large veins of both arms. This eliminates the factor of dilution of the contrast material by blood from the opposite innominate vein when only one injection is made and, of course, increases the bolus effect of the contrast material into the circulation. Speed of injection is also facilitated by elevating the arms and having the patient perform respiratory maneuvers.

The time of roentgen exposure of the abdominal aortic or peripheral arteriogram is determined by the preliminary circulation time with sodium dehydrocholate (Decholin). Standard roentgen technic similar to that of intravenous pyelography, which makes use of the Bucky-Potter grid, is all that is needed for roentgenography of the abdominal aorta and its branches.

The percutaneous insertion of the Robb-Steinberg 12-gage needle stop-cock unit has previously been described.[2, 6] In the absence of a large vein, it may be necessary to perform a cut-down for insertion of the needle. The position of the cannula is then secured by adhesive tape. To make certain that the cannula is properly seated in the vein, an injection of normal physiologic saline to safeguard against extravasation is advisable. The patient is then briefed about the technic of the examination and is instructed about breathing during the examination.

The determination of the preliminary circulation time with the patient supine will serve as a good rehearsal of the patient's participation in the test. Three milliliters of a 20 per cent solution of Decholin are mixed with 15 ml. of saline in a 50-ml. syringe and attached to one of the cannulas. The arm is then elevated, making certain that it is relaxed at the shoulder (this avoids physiologic obstruction of the subclavian vein underneath the first rib). The stop-cock is then opened and the patient is instructed to "breathe out" gently. Then he is asked to "breathe in" making certain that only a moderate breath is taken, for it is important to avoid the Valsalva maneuver, which tends to delay circulation into the heart. Injection of the Decholin-saline mixture is made simultaneously with the direction to "breathe in." This is also the signal for the assistant to start the stop-watch. Once the injection is completed, the patient having been told to anticipate a bitter taste, he is urged to go through the motion of tasting by smacking his lips, tongue, and mouth. This automatically releases the tendency to perform the Valsalva maneuver. The onset of the bitter taste is then recorded by stop-watch. The modified circulation time from arm to

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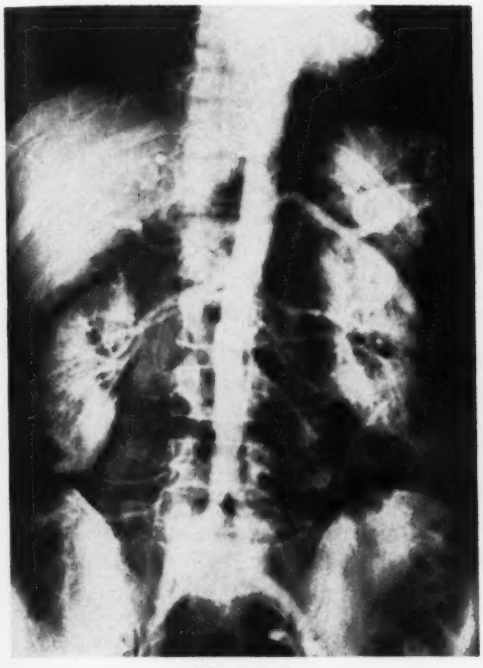


Figure 1A

Abdominal aortoiliac arterial circulation in a 50-year-old man.

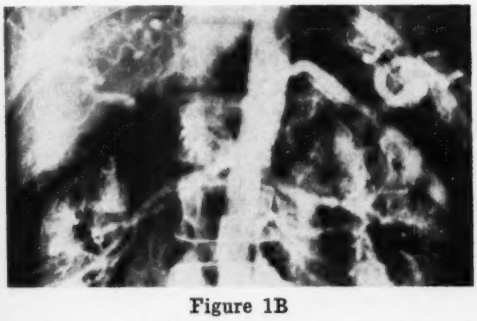


Figure 1B

Enlargement of figure 1A to show detailed visualization of the celiac axis and renal arterial vasculature.

tongue is used as a guide for the starting time of the roentgen exposure for the abdominal aorta. If the accuracy of this determination is uncertain, a repeat circulation-time determination is done. The exposure for abdominal aortography is prolonged to 2 or 3 seconds and begins about one-half second after the circulation time.

The patient is told to anticipate an intense wave of heat soon after injection of the contrast

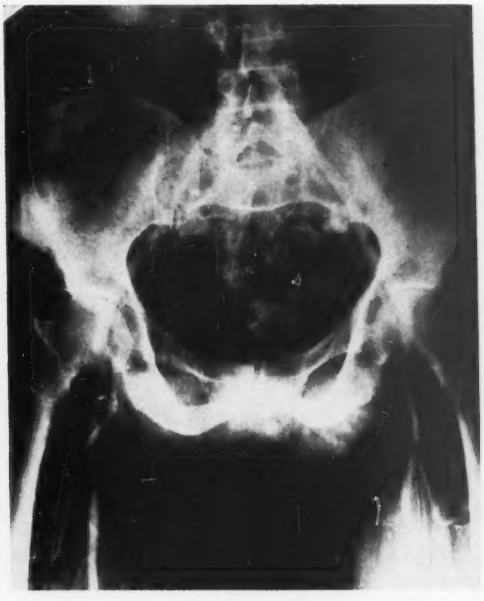


Figure 1C

The peripheral vascular system from the bifurcation of the abdominal aorta to the mid thigh regions.

Figure 1D

The normal superficial femoral arterial tree.

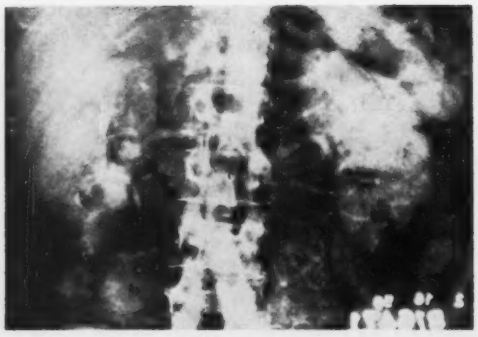


Figure 2A

Hypertension due to a renal artery aneurysm in a 50-year-old man. Intravenous abdominal aortogram showing the right renal artery aneurysm (arrow).

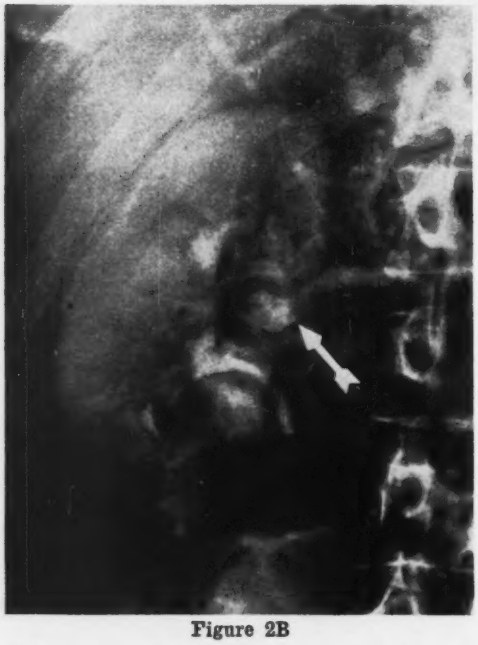


Figure 2B

Enlargement of figure 2A better to show the aneurysm in the hilus of the kidney (arrow).

medium and is assured that it will quickly pass. All is then ready for aortographic study. The special (12 gage) Robb-Steinberg syringes are loaded with concentrated organic iodide contrast material, the amount depending on the weight of the patient. A dose of 1 ml. per kilogram of body weight, divided equally for injection into each arm, is advised. Up to 50 ml. in each arm may be necessary

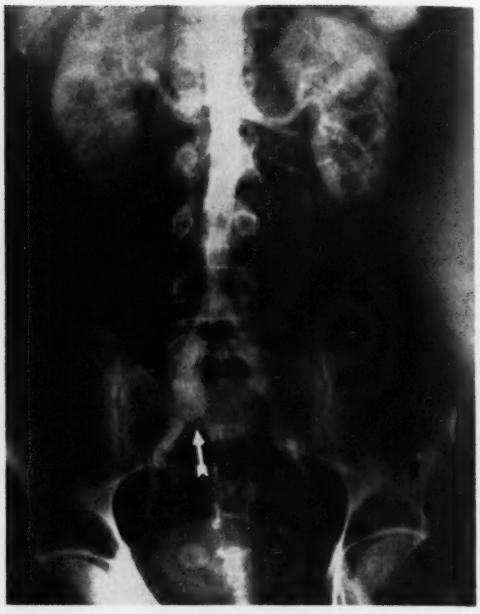


Figure 3

Incidentally discovered right common iliac artery aneurysm (arrow) in a 51-year-old man with hypertension (160/110 mm. Hg).

for obese patients over 200 pounds. The syringes are then attached to the cannulas, the stop-cock is opened, and the arms are elevated with a physician standing on a platform on each side of the patient. At the signal, "breathe in," the technician starts the stop-watch. The simultaneous injections are made rapidly and completed in 1½ to 2 seconds. Because of viscidity the concentrated contrast agent may be difficult to inject rapidly unless the mixture is warm. The patient is then told to "breath naturally." Two or 3 seconds prior to the selected exposure time, the patient is ordered to "stop breathing." A 2-second roentgen exposure for abdominal aortography is then made while the patient holds his breath. If peripheral arteriography is desired, another exposure of 3 seconds' duration may be made either with a portable roentgen apparatus or with another x-ray tube. The standard grid-cassette technic for lower extremity roentgenography suffices. If, after inspection, the roentgenogram proves satisfactory, the cannulas may be removed and a tight, temporary bandage applied. There should be no hesitancy in repeating the injection after a short interval, if the patient has tolerated the procedure. Also, if the peripheral circulation at the bifurcation of the iliac arteries is desired, the Bucky grid

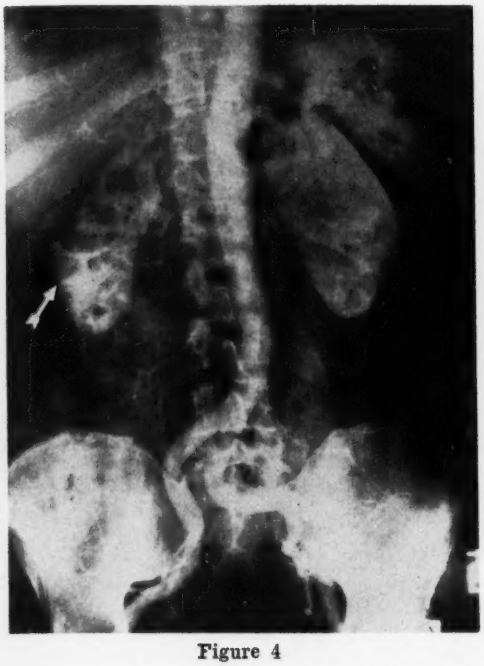


Figure 4

Intravenous abdominal aortogram of a 40-year-old man with an 8-year history of hypertension (145/110 mm. Hg) and contracted right kidney (arrow). Note the tortuosity of the abdominal aorta and common iliac arteries. Nephrectomy revealed chronic pyelonephritis and arteriosclerosis of the kidney, following which there was some decrease in blood pressure.

cassette may be shifted to include the extremities and another injection made.

Results

Since March 31, 1959, when the method of rapid, bilateral, and simultaneous intravenous injections of concentrated contrast agents for visualization of the entire cardiovascular system began, 350 patients have been studied. Of these, 67 patients had simultaneous double injections for reasons other than for abdominal aortography; some during the development of the technic of carotid-vertebral arteriography soon to be published,[9] and others for visualization of the cardiovascular system. The latter because visualization of the cardiovascular structures was enhanced when chronic heart failure, or aortic valvular

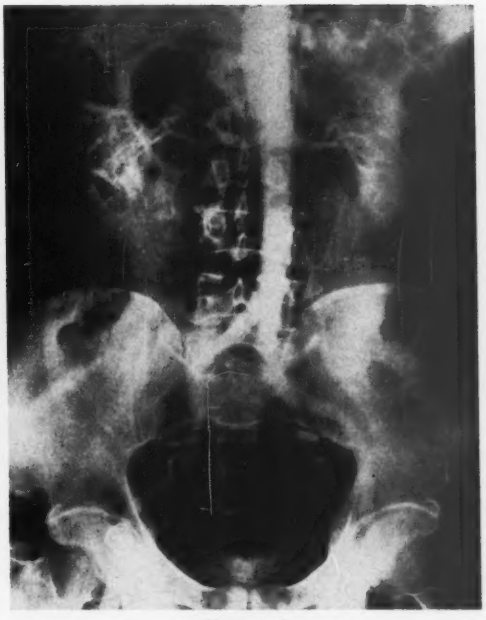


Figure 5

Arteriosclerotic tortuosity of the aortoiliac arterial system in a 62-year-old man with normal blood pressure (140/85 mm. Hg).

disease, or both existed. Two hundred and eighty-three patients have had intravenous abdominal aortography and peripheral arteriography and form the basis of this report. Failure to visualize the abdominal aorta occurred in only two instances. The first was in an 81-year-old man with chronic heart failure, atrial fibrillation, and aortic and mitral insufficiency with a modified (Decholin) circulation time of 34 seconds. The other was in a 55-year-old man with advanced silicosis, cor pulmonale, and congestive heart failure. In the latter, although the first series of double injections failed to show the abdominal aorta, a repeat single injection for angiocardiography revealed a massive pericardial effusion as well as a dilated pulmonary artery and cardiac chambers due to congestive heart failure.

In 32 cases a normal abdominal aorta and peripheral arterial system was revealed (fig. 1). The patients in this group had been referred because of an unusually pulsatile aorta

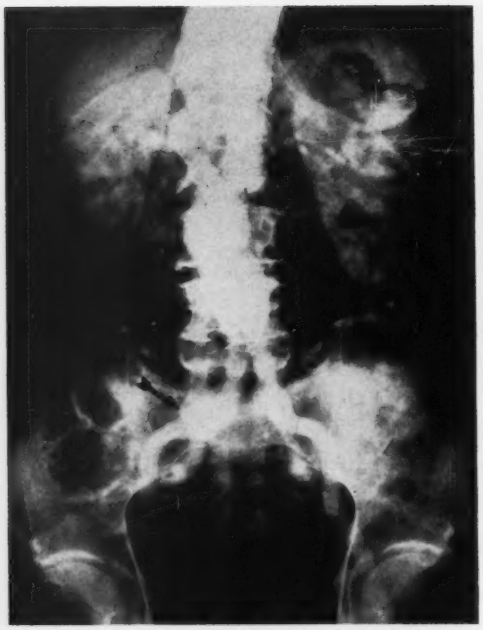


Figure 6A

Fusiform abdominal aortic aneurysm beginning just below intact renal arteries. A right common iliac artery (arrow) was also resected and replaced by a graft.

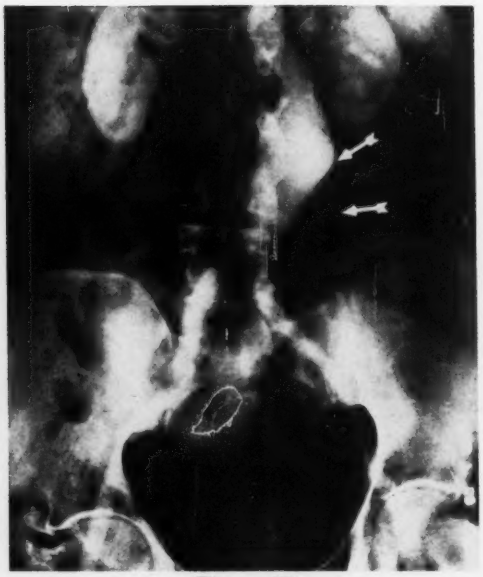


Figure 6B

Sacciform abdominal aortic aneurysm (upper arrow) well below the renal arteries, and surrounded by a large thrombus containing calcium (lower arrow) in a 63-year-old man.

simulating an abdominal aortic aneurysm. In one case, a large firm mesenteric lymphoma exaggerated and transmitted the abdominal aortic pulsations. In another, a previous laparotomy for ileitis had caused abdominal peritoneal adhesions, which had transmitted the pulsations of the aorta.

The remaining 251 patients with disease of the abdominal aorta and its branches were classified according to the major lesion. Abdominal aortography was performed in 62 hypertensive patients, chiefly to determine if renal arterial deformities were present. In four instances, renal artery stenosis with post-stenotic dilatation of the distal portion of the renal artery was discovered. In three of these, splenectomy with anastomosis of the splenic artery to the distal post-stenotic left renal artery was followed by return of the blood pressure to normotensive levels.[10] In two hypertensive patients, right renal artery aneurysms, one a saccular renal artery aneurysm, (fig. 2) was visualized.[11] Aortic aneurysms were also encountered in hypertensive patients, but these were classified with the aortic aneurysm group because the major lesion was the aneurysm. A hypertensive patient with an isolated right iliac aneurysm is shown in figure 3. Other patients with hypertension were found to have striking tortuosity of the abdominal aorta and iliofemoral arterial system, a finding usually due to arteriosclerosis, but they were included in the hypertensive groups; the tortuosity was considered to be an arteriosclerotic complication of hypertension (fig. 4).

Twenty-four patients without hypertension had pronounced arteriosclerotic abdominal aortic and iliofemoral tortuosity (fig. 5). Often, the reason for referral of these patients was an unusually pulsatile aorta. Indeed, in three instances, arteriosclerotic plaques seen in the conventional abdominal film were located in the walls of a tortuous

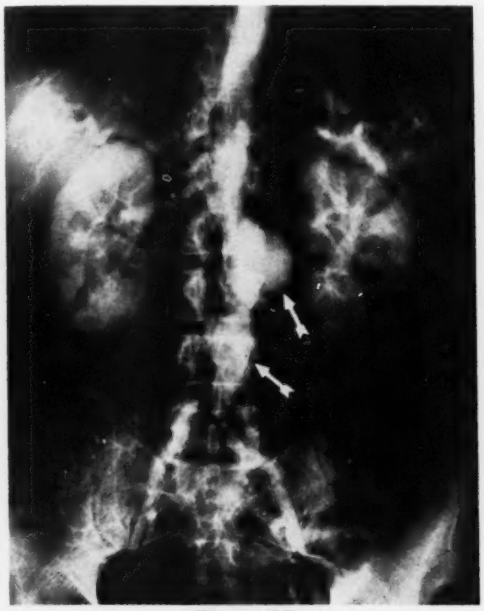


Figure 6C

Double saccular aneurysms (arrows) in a 51-year-old man.

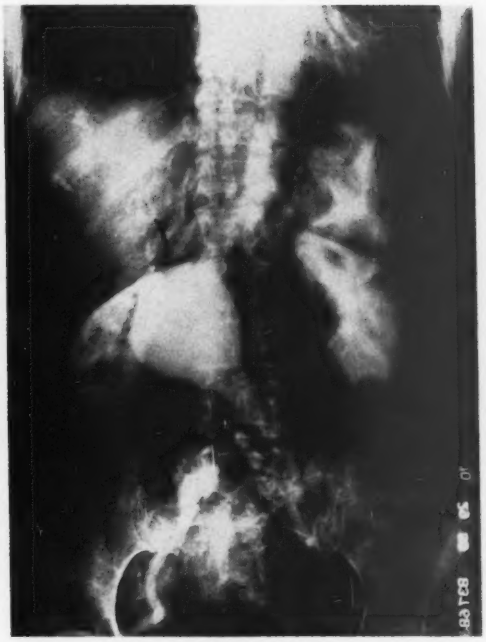


Figure 6D

Huge saccular aneurysm (arrow) without a thrombotic wall in a 74-year-old woman.

but intact abdominal aorta that had been mistaken for the calcified thrombus wall of an aneurysm.

Arteriosclerotic abdominal aortic aneurysms without serious peripheral vascular involvement were visualized in 24 patients (fig. 6). Thirteen additional patients with arteriosclerotic abdominal aortic aneurysms had pronounced peripheral vascular disease; the poor run-off denoted a bad prognosis (fig. 7).[12] A huge saccular aneurysm of the lower descending thoracic aorta due to syphilis is shown in figure 8.

Arteriosclerotic endarteritic involvement of the abdominal aorta and common iliac arteries without significant peripheral vascular disease was present in 31 patients. Arteriosclerotic peripheral vascular disease (usually occlusion) as well as arteriosclerotic abdominal aortic endarteritis were found in 11 cases (fig. 9). Severe chronic arteriosclerotic thrombotic occlusion of the abdominal aorta was demonstrated in 13 patients (fig. 10). Peripheral arteriosclerotic vascular disease with arterial occlusions but without demonstrable abdominal aortic involvement was present in 47 patients (fig. 11).

A miscellaneous group totaling 23 patients, comprised various, albeit unusual conditions such as: arteriosclerotic splenic artery aneurysms, 4 cases,[13, 14] an aberrant spleen (fig. 12), a ruptured spleen,[15] and an arteriosclerotic hepatic artery aneurysm.[14] Four patients had arteriovenous fistulas. One followed laminectomy for a ruptured lumbar disk (fig. 13).[16] Another was caused by a gun-shot wound of the left leg, while the remaining two were congenital, also involving the left leg.

A congenitally single hypertrophied right kidney was found in one patient. Two patients with peripheral vascular disease also had had nephrectomies several years prior to arteriography; the remaining kidney was markedly enlarged. In intrinsic disease of the kidneys, the abdominal aortography studies were often supplemented by nephrotomography.[17] In

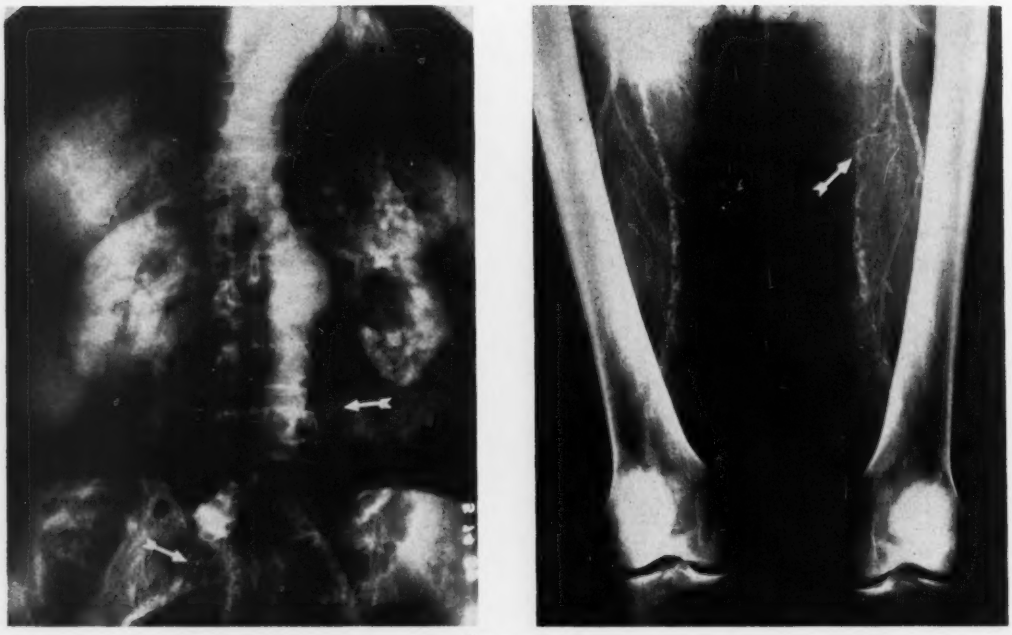


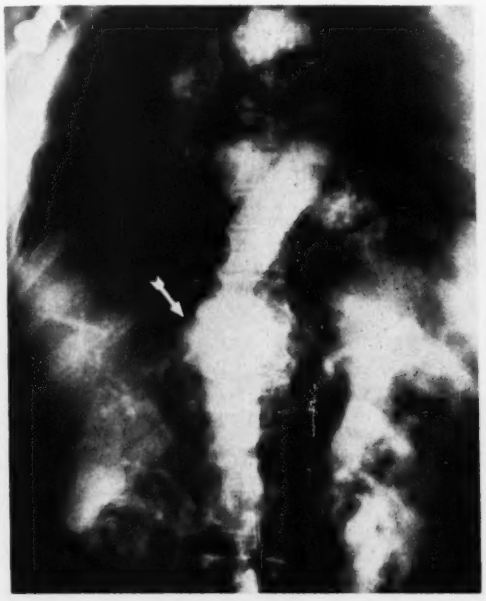
Figure 7

Huge arteriosclerotic aneurysm of abdominal aorta with peripheral vascular disease and old myocardial infarctions in a 70-year-old man. Left. *Sacciform abdominal aortic aneurysm surrounded by a large calcium-lined thrombus (arrow). Lower arrow on the right side points to occlusion of right common iliac artery.* Right. *The peripheral arterial circulation showing well-developed superficial and profunda femoral arteries, especially on the right side. Note the calcifications of the poorly opacified superficial femoral arteries and the communication of the left profunda femoral artery with the calcified superficial femoral artery (arrow). (Operation was not advised.)*

nine patients a nonfunctioning kidney (3 cases), hydronephrosis (1 case), and pyelonephritis (5 cases) were revealed. A patient with a huge fibromyxosarcoma showed unusual displacement of the right kidney (fig. 14). Finally, an anomalous abdominal aortic communication to the right lower lobe of the right lung was demonstrated in a 10-year-old boy with anomalous pulmonary venous drainage of the right lung into the inferior vena cava associated with bronchiectasis; the abdominal aortic as well as the cardiovascular structures were visualized via the intravenous route.

Discussion

The advantages of securing abdominal aortography and peripheral arteriography by intravenous injection are obvious. No longer need there be hesitancy in attempting to visualize these structures, since the complications of arterial puncture, especially those of translumbar aortography,[18-25] are entirely avoided. Now that surgical excision of aneurysms and replacement by homografts and synthetic materials are possible, aneurysmal and occlusive disease of the abdominal aorta and its branches is no longer of merely academic interest. With elimination of the necessity for anesthesia and the hazards of direct abdominal aortic puncture, greater use of intravenous aortography for diagnosis of disease of this system will be forthcoming. Furthermore, the benefits and results of surgery can be readily demonstrated, and the complications and shortcomings of surgical procedures may also be evaluated.



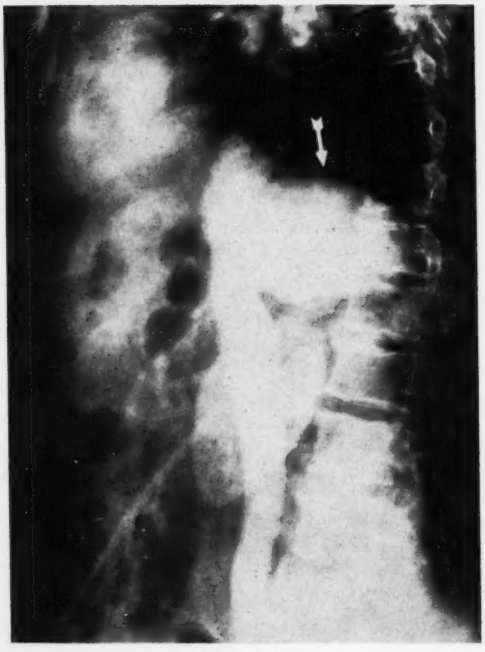


Figure 8

Huge syphilitic aneurysm of the thoracolumbar descending aorta in a 63-year-old man. Top. *Frontal view of aneurysm (arrow).* Bottom. *Lateral view showing that the aneurysm (arrow) was located behind the aorta.*

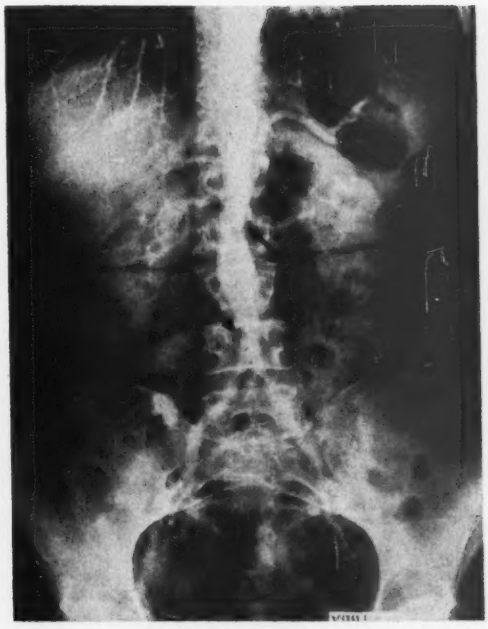
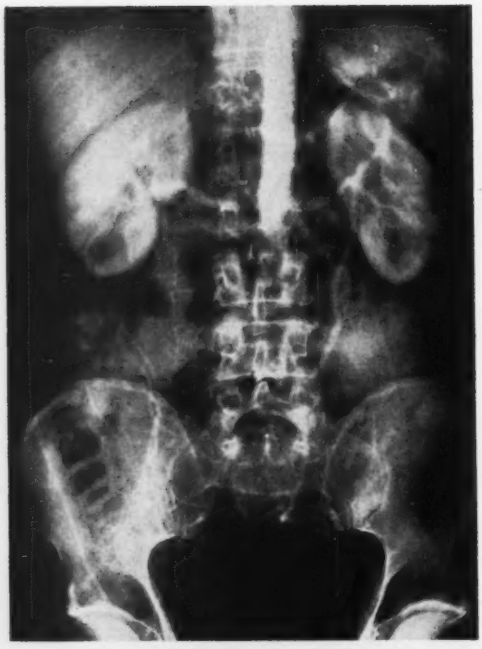


Figure 9

Arteriosclerotic abdominal aortic endarteritis and peripheral vascular disease in a 52-year-old woman with marked irregularity and stenosis of the abdominal aorta (arrows). Diminution of blood flow at the bifurcation of the aorta is evident.

Since the principles of visualizing the thoracic aorta angiocardiographically are similar to those that apply to the abdominal aorta, it is important to pay close attention to the details of the method of angiocardiography. While retrograde aortography may be indicated for coronary arteriography, the differentiation between a patent ductus arteriosus and an aorticopulmonary window, in the differential diagnosis of a ruptured aortic sinus and a coronary arteriovenous fistula, and for demonstration of mitral insufficiency and aortic valvular disease, it need not be used for routine visualization of the aorta.[7] Failure to opacify the thoracic aorta angiocardiographically is usually due to disregard of the principles of speed of injection, proper positioning of the patient, and attention to roentgenographic details.[2, 6]

The concentrated contrast materials now available commercially are well tolerated in-



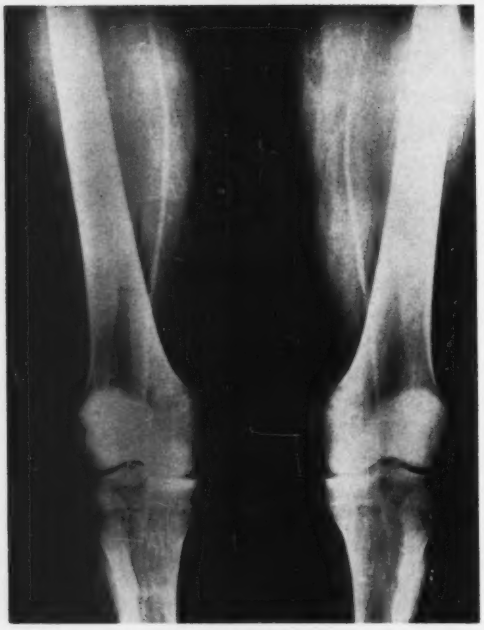


Figure 10

Thrombotic occlusion of the abdominal aorta in a 53-year-old man. Top. *The complete abdominal aortic occlusion just below intact renal arteries is evident. Note the profuse and well-established collateral arteries.* Bottom. *Despite absent femoral pulses there is an intact, though hypoplastic, peripheral vascular system. Endarterectomy of the abdominal aorta was followed by good femoral pulses and complete subsidence of claudications of the hip and buttocks.*

travenously even in large doses.[26] Thrombophlebitis has not proved to be troublesome. In several instances double injections have been tolerated without apparent venous damage. The usual reaction to the simultaneous double dose is mild and transient and very much like that in angiocardiography with a single injection, except that there is a more intense flush and a greater sensation of heat, traveling from head to toe. The reaction is probably also aggravated by the supine position, since reactions are usually less pronounced in erect patients during angiocardiography. Vomiting does not occur when the study is made during the fasting state (the meal prior to the examination is omitted). Reactions to the contrast material can be markedly diminished if there is a calm, reassured, nonapprehensive attitude.[27] In contrast to translumbar aortography, where there is danger to the kidney when the aorta is occluded by thrombus, visualization of the renal arteries via the intravenous routes does not harm the kidneys.

Two severe reactions and one fatality have occurred in the first 350 patients who had double injections of concentrated organic iodides. A 16-year-old boy developed severe orbital edema after one double injection; this promptly subsided after antihistamine therapy. Another patient, a 38-year-old man, had fever, leukocytosis, and mild hypotension after three double injections lasting for 6 hours only. A 74-year-old man with moderately severe peripheral, cardiovascular, and cerebral arteriosclerosis had no immediate reaction to two double injections of contrast material. Six hours later there was sudden onset of pulmonary edema. The electrocardiogram did not show arrhythmia or myocardial infarction. At autopsy, 41 hours after the intravenous study, advanced arteriosclerotic, cerebral, cardiac, abdominal aortic, and pe-

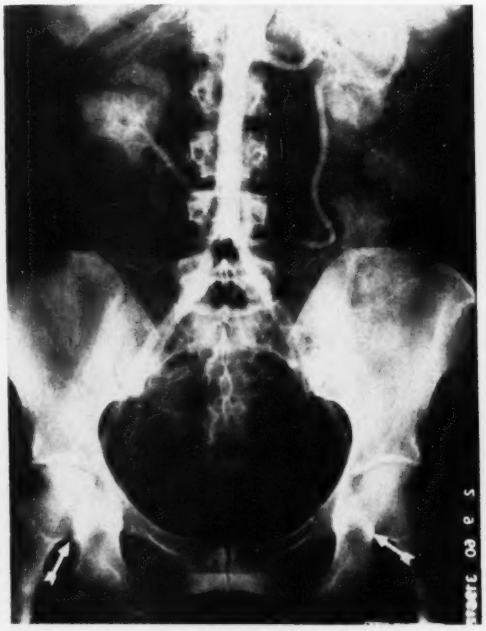


Figure 11A

Severe intermittent claudication of both legs in a 38-year-old woman with bilateral occlusion of the common femoral arteries (arrows). Note that the renal artery on the right arises from the common iliac artery while the splenic artery originates from the left common iliac artery.

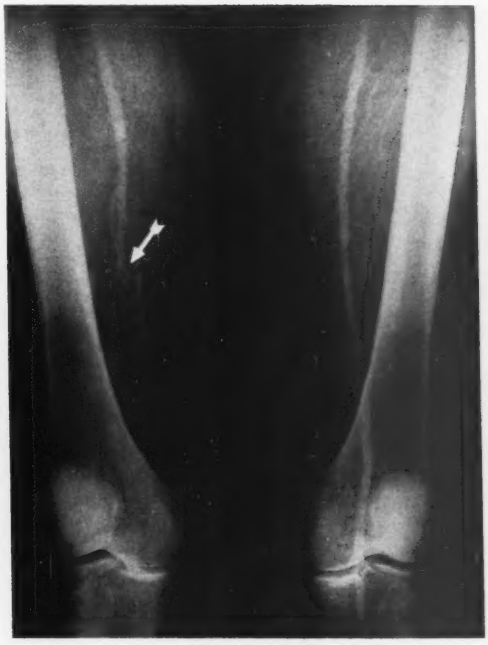


Figure 11B

Severe intermittent claudication of the right leg after one half block due to occlusion of the right superficial femoral artery (arrow) in a 53-year-old man.

ripheral vascular disease was demonstrated. The immediate cause of death could not be ascertained. Two other fatalities have occurred in our series of 4,700 patients studied for angiocardiography with a single injection. The first, a 56-year-old woman, had postradiation pericardial effusion and died 5 hours after injection of contrast material.[28] The other, a 6-year-old child with primary pulmonary hypertension, died immediately after injection of the media.[29] Since the patients undergoing angiocardiography usually have serious circulatory handicaps, the rare fatality due to the procedure should not contraindicate the study. Furthermore, because it offers the prospect of clarifying a diagnosis and deciding whether a case is operable, the risk involved in angiocardiography is certainly less than the risks of not treating or incorrectly treating the disease.

The roentgen exposure time of the abdominal examination has been 2 seconds. In contrast to cardiac chamber and great vessel visualization, which requires short exposure times,[6] the abdominal aortic and peripheral arterial exposure times may be prolonged. The present technic results in only one contrast roentgenogram of the abdominal aorta. A simultaneous angiogram of the peripheral arterial tree can be easily made by another exposure of the lower extremities (with suitable coning to prevent fogging of the abdominal roentgenogram) with a portable roentgen unit. Since only three or, at the most, four films (including preliminary positioning and pyelographic roentgenograms) are exposed during a contrast study of the abdominal aorta, the amount of radiation to the patient is low. The physicians making the injection receive very little exposure if the roentgen beam is suitably collimated and conventional

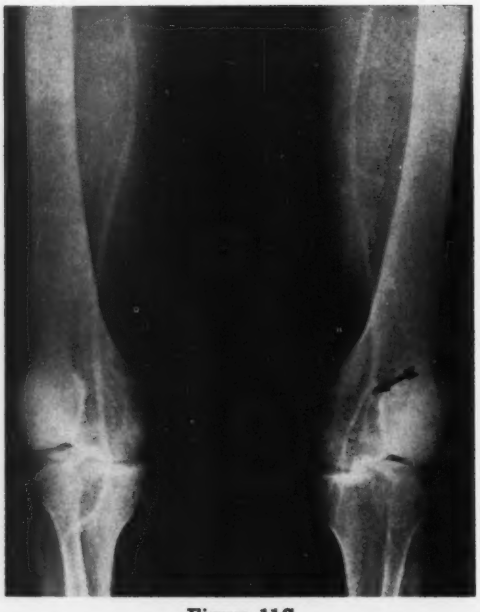


Figure 11C

Occlusion lower end of the left superficial femoral artery (arrow) in a 33-year-old man with disabling claudication of the left leg.

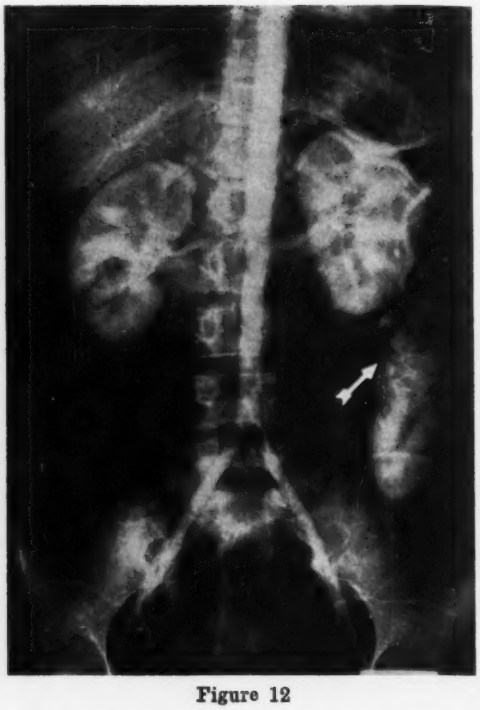


Figure 12

An aberrant spleen (arrow) with a dangling splenic artery was responsible for a left lower quadrant mass in a 33-year-old woman.

protective garments are worn. As a further precaution, the arm, once the injection is completed, may be placed at the side of the patient on the table and the operators can move to a shielded area. Sufficient time for this is afforded because the exposure of the roentgenogram is made 10 seconds or more after the beginning of injection; the injection is usually concluded at the end of 2 seconds.

The personnel for performance of abdominal arteriography via the intravenous route consists of two physicians who make the injection and a technician. This is much less formidable than translumbar aortography, where the injector must maintain sterile precautions necessitating a trained attendant. If general anesthesia is required for the translumbar study, another trained nurse or anesthesiologist is needed. Since local anesthesia is used only for insertion of the cannulas for the intravenous method, general anesthesia is not needed.

Determination of the preliminary modified circulation time with Decholin prior to the injection of the contrast material is advised for every patient. This is not only indicative as to whether there is obstruction (physiologic or pathologic) to blood flow into the heart but may also predict inability to secure a satisfactory study. Delay of passage of the contrast material occurs in cases of pulmonary disease associated with cor pulmonale, some types of congenital heart disease (Ebstein's anomaly, aortic stenosis), congestive heart failure, and valvular disease such as mitral stenosis and aortic stenosis or regurgitation. Rarely, in such instances, abdominal aortography may not be successful because of dilution of the contrast material and disruption of its continuity. Fortunately, patients requiring abdominal arteriography are usually free of congenital heart disease, congestive heart failure, and valvular heart disease.

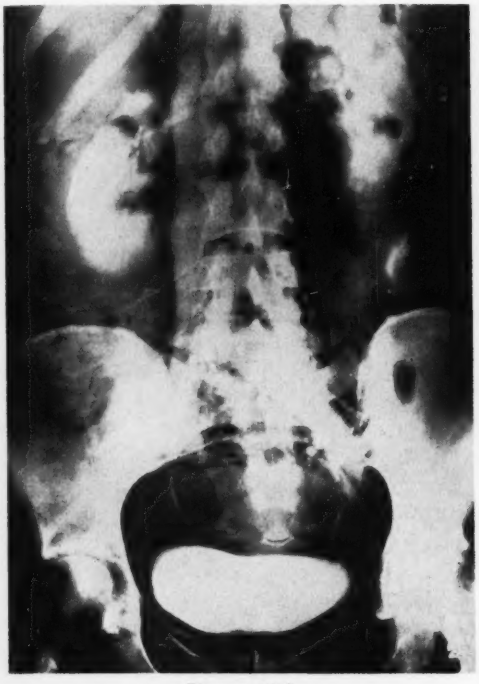


Figure 13A

Right common iliac arterial-inferior vena caval fistula in a 47-year-old woman following laminectomy for intervertebral disk. The intravenous abdominal aortogram.

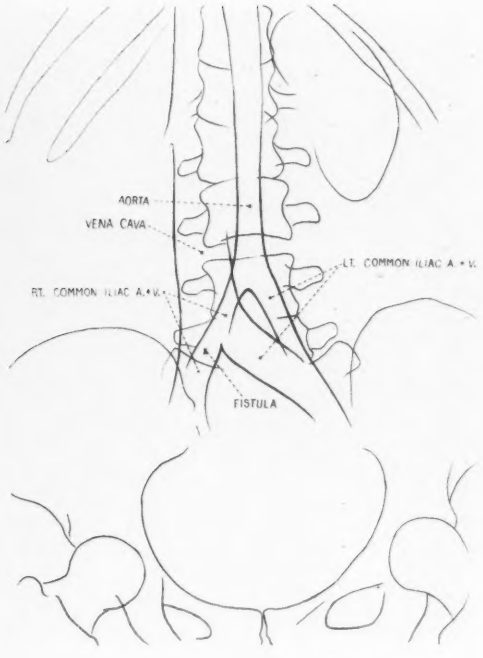


Figure 13B

Tracing of figure 13A.

A single bilateral intravenous injection succeeded in satisfactorily visualizing the abdominal aorta and peripheral vascular system in 65 per cent of the patients. In the remainder, another double injection was necessary. Failure of the patient to suppress breathing during the exposure of the abdominal aorta causing blurring of the renal arterial circulation was the prime reason for a repeat examination. Another, was the performance of the Valsalva maneuver, especially in apprehensive individuals. Aneurysms of the abdominal aorta apparently cause marked delay in blood flow and the usual exposure time of the abdominal film (one half second) after the modified Decholin circulation time often failed to fill the aneurysm completely. Accordingly, when an abdominal aortic aneurysm is suspected, exposure of the abdominal aortic roentgenogram should begin 3 or more seconds after the Decholin circulation time.

Contraindications to intravenous abdominal aortography are rare. The patient should be cooperative and well enough to lie on a roentgen table for at least one-half hour. Unconscious or anesthetized patients may, however, be examined successfully; experience with angiocardiography indicates that anesthetized patients may be injected rapidly without the aid of respiratory maneuvers. In such instances an objective type of circulation time may have to be used in order to estimate the time of exposure of the abdominal roentgenograms. No longer need azotemia contraindicate study of the circulatory system using organic iodides. Indeed, such compounds are used widely for diagnosis of kidney disease, even when uremia is present. Diagnosis of an obstructive urologic lesion amenable to surgical alleviation or cure far outweighs the risk, if any, of adding to nitrog-

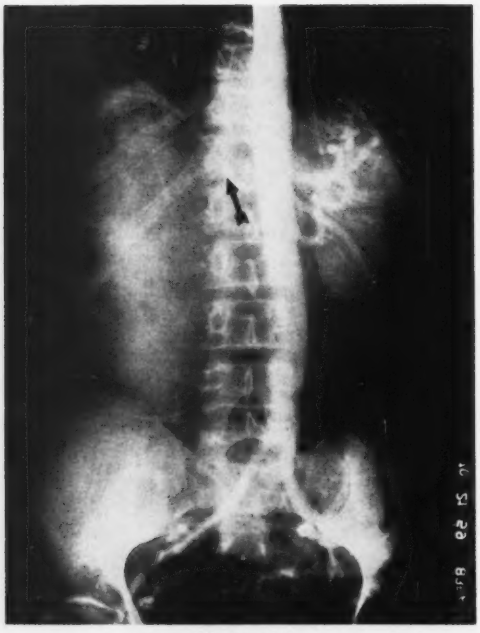


Figure 14

Huge lipomyxosarcoma causing marked upward displacement of the right renal artery (arrow).

enous wastes in the blood. Furthermore, in the presence of poor renal function, much of the contrast material is excreted in the biliary tract.

The increasing use of splenoportography without harm in patients with cirrhosis of the liver also demonstrates that advanced liver disease is not a contraindication to the injection of the organic iodide compounds into venous channels. Since the organic contrast compounds are securely bound to the iodide molecule, patients allergic to the iodides need not be deprived of diagnostic studies with such agents. In our large experience many allergic patients have tolerated angiocardiographic and urographic studies without ill effects.[27] Finally, there remains the rare individual who reacts severely to the radiopaque material in an anaphylactic fashion. Since preliminary testing, whether intradermal, ocular, oral, or intravenous, does not designate the severe reactor, routine pretesting or premedication need not be done. If there is a clear indication for study of the circulatory system, the rare fatality must be accepted as an unavoidable risk. However, the availability of emergency treatment for severe reactors will further cut the risk.[27] Good clinical judgment based on experience is all important for selection of the patient suitable for study; this will also detect the high-risk patient who requires special facilities for the intravenous injection.

Complete opacification of the circulatory system, total body intravenous angiography, in man is now feasible. To accomplish this ideally, biplane angiocardiography at onset of the intravenous injection will provide studies of the entire cardiovascular system. Cerebral angiography, preferably biplane, may then be secured beginning with the systemic (Decholin) circulation time. Soon after (one half to one second), roentgen exposure of the abdomen will visualize the abdominal aorta. Finally, the peripheral circulation (the exposure time commencing at the conclusion of the abdominal aorta study) can be visualized. Motion of the various circulatory components may also be had by cineangiography.

Although a total body survey of the circulatory system may be of limited clinical value, the data may prove invaluable for physiologic study. Continuous electrocardiography during intravenous injection will relate the opacification of the various systems to the cardiac cycle. Biplane studies will permit volumetric determinations of the cardiac chambers and great vessels and the cardiac output. Variations of the circulatory system with systole and diastole and propagation of the pulse can also be evaluated.

The large variety of abdominal aortic and peripheral vascular disease encountered in the series of cases herein described well illustrates the value of intravenous abdominal aortography. In this report of 350 patients who had bilateral intravenous injections, 101 had abnormalities of the abdominal aorta and its branches. This figure results when the two patients who could not be visualized, the 67 who were primarily studied for carotid-vertebral arteriography and cardiovascular

angiography, and the 32 patients with normal abdominal aortas are subtracted from the total number of cases.

Data derived from translumbar arteriography have shown that a significant percentage of patients can be discovered to have a renal cause for hypertension.[30, 31] Renal artery aneurysm (fig. 2) and stenosis of the renal artery with post-stenotic dilatation of the distal arterial segment have also been demonstrated with the intravenous method of abdominal aortography. A hypoplastic right kidney was also revealed (fig. 4). In another hypertensive patient, a right common iliac artery aneurysm was found (fig. 3).

Arteriosclerosis of the abdominal aorta and its branches is a common disease. The diagnosis of an abdominal aortic aneurysm often depends upon discovery of a pulsatile abdominal mass or calcifications adjacent to the lumbar spine in the abdominal roentgenogram. Routine palpation of the peripheral arterial system will often be rewarding in the evaluation of the hip and leg pains.[23, 32] Tortuosity of varying degrees is a common manifestation of arteriosclerosis of the abdominal aorta (figs. 4 and 5). Arteriosclerotic abdominal aortic aneurysms can be of all sizes and shapes (figs. 6 and 7). By demonstrating the run-off into the legs, practical and valuable preoperative data can be provided by intravenous aortography (fig. 7B).

The diagnosis of arteriosclerotic occlusive disease of the abdominal aorta and peripheral vascular system although easily established clinically requires angiography for adequate surgical treatment.[23, 32] Because translumbar aortography is especially dangerous when there is occlusive disease of the abdominal aorta, translumbar aortography has been abandoned in many centers.[23] Accordingly, intravenous abdominal aortography can provide a significant and important aid in the diagnosis and treatment of chronic insidious occlusive disease of the abdominal aorta and peripheral vascular system (figs. 9, 10, and 11). Arteriosclerotic aneurysms of the splenic artery were encountered four times; a hepatic artery aneurysm, once in this series.[13, 14]

Penicillin has made syphilitic and mycotic aneurysms of the abdominal aorta and branches rare. Actually, the etiologic diagnosis is only of academic interest, since the treatment, as in the case of the arteriosclerotic aneurysm, is the same; namely, resection of the aneurysm after suitable bypass procedures are provided and replacement by a plastic prosthesis. Figure 8 is an example of a huge syphilitic aneurysm of the thoracoabdominal aorta, the only example of an aneurysm due to an infectious agent in the series.

Trauma to the abdominal aorta and its branches was encountered in four instances. An aortico-inferior vena caval fistula was demonstrated in a patient in heart failure following laminectomy for an intervertebral disk (fig. 13).[16] Gunshot wounds in the legs were responsible for two other arteriovenous fistulas of the popliteal vessels demonstrated with intravenous peripheral arteriography. Delayed rupture of the spleen was demonstrated in one case.[15]

Congenital anomalies demonstrated by intravenous abdominal aortography consisted of a right renal artery originating from the right iliac artery and the splenic artery arising from the left common iliac artery (fig. 11A). Congenital arteriovenous fistulas involving the superficial femoral artery and vein of the left leg were visualized in two cases. A dangling spleen was demonstrated to be the cause of a left lower abdominal mass (fig. 12). Finally, marked displacement of the abdominal aorta and right kidney was revealed in a patient with retroperitoneal fibromyxosarcoma (fig. 14).

Summary and Conclusions

A practical intravenous method of abdominal aortography and peripheral arteriography, making use of physiologic principles learned during angiocardiography, is described which can be performed in the average hospital. This method has distinct advantages over the translumbar abdominal aortic injection route, which has sometimes been

associated with serious complications and occasionally death.

Rapid and simultaneous injection of concentrated organic iodides can be made by injection into both arms with special syringes attached to Robb-Steinberg cannulas. If dosages of 1 ml. per kilogram of body weight are used, the reaction to injection of large quantities of the contrast material will be well tolerated. Since conventional roentgen equipment is all that is required for the intravenous method of abdominal aortography and peripheral arteriography, the study can be performed in almost every radiologic department.

Aneurysmal and occlusive disease of the abdominal aorta and branches can be readily diagnosed, facilitating the appropriate treatment for each patient. Traumatic, congenital, and neoplastic diseases of the abdominal aorta can also be demonstrated, permitting a preoperative view of the lesion and determining if it is amenable to surgical repair.

Finally, modification of the Robb-Steinberg method of intravenous injection of concentrated contrast material, by making a double simultaneous injection, renders possible the visualization not only of the central cardiovascular system (the great veins, the chambers of the heart, the pulmonary circulation, and the thoracic aorta) but also the abdominal aorta, peripheral arteries, and cerebral vessels. Thus, total visualization of the circulatory system is achieved—total body angiography.

References

1. Robb, G. P., and Steinberg, I.: A practical method of visualization of the chambers of the heart, the pulmonary circulation and the great blood vessels in man. J. Clin. Invest. **17**: 517, 1938.
2. Robb, G. P., and Steinberg, I.: Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man: A practical method. Am. J. Roentgenol. **41**: 1, 1939.
3. Robb, G. P., and Steinberg, I.: Visualization of the chambers of the heart, the pulmonary circulation and the great blood vessels in man: Summary of method and results. J.A.M.A **114**: 474, 1940.
4. Steinberg, I., Finby, N., and Evans, J. A.: A safe and practical method of intravenous abdominal aortography, peripheral arteriography, and cerebral angiography. Abstract, Circulation **20**: 774, 1959.
5. Steinberg, I., Finby, N., and Evans, J. A.: A safe and practical intravenous method for abdominal aortography, peripheral arteriography, and cerebral angiography. Am. J. Roentgenol. **82**: 758, 1959.
6. Dotter, C. T., and Steinberg, I.: Angiocardiography. New York, Paul B. Hoeber, Inc., 1951.
7. Steinberg, I., and Finby, N.: The importance of angiocardiography for visualizing the thoracic aorta. Arch. Surg. **74**: 29, 1957.
8. Steinberg, I.: Editorial: Intravenous angiocardiography; the twentieth year. Am. J. Roentgenol. **81**: 886, 1959.
9. Steinberg, I., and Evans, J. A.: Technique of intravenous carotid-vertebral arteriography. Am. J. Roentgenol. In press.
10. Steinberg, I., and Goldsmith, E. I.: Intravenous abdominal aortography in diagnosis and treatment of renal hypertension. To be published.
11. Steinberg, I., Finby, N., and Evans, J. A.: Value of intravenous abdominal aortography in the diagnosis and differential diagnosis of aneurysms of the splenic, hepatic and renal arteries. To be published.
12. Steinberg, I., and Moore, S. W.: Intravenous abdominal aortography in treatment of abdominal aortic aneurysms. J.A.M.A. **175**: 446, 1961.
13. Steinberg, I., and Lord, J. W., Jr.: Splenic artery aneurysm: Diagnosis by intravenous abdominal aortography. J.A.M.A. **174**: 73, 1960.
14. Steinberg, I.: Diagnosis of aneurysms of the hepatic and splenic artery by intravenous abdominal arteriography. New England J. Med. **263**: 341, 1960.
15. Steinberg, I., and Karl, R.: Diagnosis of ruptured spleen by intravenous abdominal aortography. Am. J. Roentgenol. **84**: 902, 1961.
16. Steinberg, I., Glenn, F., Carter, S. T., and Lukas, D.: Angiographic and hemodynamic studies of a post-laminectomy iliac arterial and inferior vena caval fistula. Cure by excision and suture of the lesion. Am. J. Med. In press.
17. Chynn, K. Y., and Evans, J. A.: Nephrotomography in the differentiation of renal cyst from neoplasm. A review of 500 cases. J. Urology **83**: 21, 1960.
18. Crawford, E. S., Beal, A. C., Jr., Moyer, J. H., and De Bakey, M. E.: Complications of

aortography. Surg., Gynec. & Obst. **104**: 129, 1957.

19. Beal, A. C., Jr., Crawford, E. S., Cowes, C. M., De Bakey, M. E., and Moyer, J. H.: Complications of aortography: Factors influencing renal function following aortography with 70 per cent urokon. Surgery **43**: 364, 1958.
20. McAfee, J. G., and Willson, J. K. V.: A review of the complications of trnaslumbar aortography. Am. J. Roentgenol. **75**: 956, 1956.
21. McAfee, J. G.: Survey of complications of abdominal aortography. Radiology **68**: 825, 1957.
22. Kincaid, O. W., and Davis, G. D.: Abdominal aortography. New England J. Med. **259**: 1017 and 1067, 1958.
23. Linton, R. R.: Peripheral vascular disease. New England J. Med. **260**: 272 and 370, 1959.
24. Wolfman, E. F., and Boblitt, D. E.: Intramural aortic dissection as a complication of translumbar aortography. Arch. Surg. **78**: 629, 1959.
25. Wilder, R. J., and Steichen, F. M.: Necrosis of the entire gastrointestinal tract following translumbar aortography. Arch. Surg. **80**: 198, 1960.
26. Steinberg, I., Finby, N., and Evans, J. A.: Ditriokon: A new cardiovascular contrast agent. Radiology **76**: 96, 1961.
27. Finby, N., Evans, J. A., and Steinberg, I.: Reactions from intravenous organic iodides compounds: Pretesting and prophylaxis. Radiology **71**: 15, 1958.
28. Steinberg, I., von Gal, H. V., and Finby, N.: Roentgen diagnosis of pericardial effusion: New angiocardiographic observations. Am. J. Roentgenol. **79**: 321, 1958.
29. Steinberg, I.: Angiocardiography in diagnosis of congenital heart disease in infancy and childhood. J.A.M.A. **170**: 772, 1959.
30. Dustan, H. P., Page, I., and Poutasse, E. F.: Renal hypertension. New England J. Med. **261**: 647, 1959.
31. Page, I., Dustan, H. P., and Poutasse, E. F.: Mechanisms, diagnosis and treatment of renal vascular hypertension. Ann. Int. Med. **51**: 196, 1959.
32. Beckwirth, R., Huffman, E. R., Eiseman, B., and Blount, S. G., Jr.: Chronic aortoiliac thrombosis: A review of 65 cases. New England J. Med. **258**: 721, 1958.

The century dating from the birth of Galileo to the death of Harvey was perhaps the most brilliant in the history of modern knowledge. The discovery of Greek texts had destroyed the conventional Aristotle, the conventional Hippocrates and Galen; since the latter part of the sixteenth century Greek had been taught in the High Schools, philosophy was born again, and men found themselves no longer the slaves but the kin of the great ancients. Telesius, Bruno, Campanella vindicated natural science and liberty of thought. Galileo taught in Padua for twenty years, including the time when Harvey graduated there; Torricelli was a pupil of the great Florentine; in 1582, on the theory of Copernicus, Gregory reformed the Calendar, and thus laid the axe to the root of astrology; by Newton terrestrial physics were established in the celestial spheres. Malpighi, who was to fulfill Harvey's discovery and foresight, was born in N.-E. Italy in the very year (1628) in which the *De motu cordis* was published. In 1626 Boyle was creating chemistry. Anatomy, which had slept since its days in Alexandria, was fully awake. The Society of the Lincei was virtually founded in 1603; the Royal Society in 1645; the Academy of France in 1656. Clinical teaching, initiated in Salerno and advanced by the *Consilia medica,* was formally established in Padua, to be pursued in Heidelberg, Leyden, and Vienna.—Thomas Clifford Allbutt, M.A., M.D. *Science and Medieval Thought.* London, C. J. Clay and Sons, 1901, p. 99.

The Frequency of Aschoff Bodies in Atrial Appendages of Patients with Mitral Stenosis

Relationship to Age, Atrial Thrombosis, and Season

By B. H. Ruebner, M.D., and J. K. Boitnott, M.D.

SMALL PORTIONS of the atrial appendage from numerous patients with mitral stenosis have been examined histologically ever since the introduction of mitral commissurotomy.[1] Although many reports on this subject have been published, there is still considerable divergence of opinion on certain questions.

Mitral valvotomy is usually performed only in the absence of clinical rheumatic activity. Nevertheless, all the authors who examined biopsies from such operations have reported a definite but variable percentage of Aschoff bodies. These are generally considered to be specific lesions indicative of rheumatic activity. This lack of correlation between histologic activity and the absence of clinical signs has not, so far, been adequately explained. The histologic criteria adopted by different observers have varied greatly. There is also uncertainty whether the atrial biopsy yields tissue representative of the rest of the heart.[2] Finally the relationship of rheumatic activity to atrial thrombosis and fibrillation requires clarification.[3, 4]

Material and Methods

The clinical and histologic findings in patients with mitral stenosis who underwent valvotomy at this hospital during 1949 to 1959 have been correlated. Three hundred and sixteen left atrial appendages were obtained during surgery. The patients had all been previously studied in order to exclude clinically active rheumatic disease. The tissue received in 4 per cent formaldehyde was trimmed into blocks. The amount of material varied considerably, so that the number of blocks obtained fluctuated from 1 to 10. Usually all the tissue was embedded. All specimens were stained with hematoxylin and eosin. Seventy-five of these were also stained by Van Gieson's method for collagen, Mallory's phosphotungstic acid-hematoxylin (PTAH), toluidine blue, and the periodic acid-Schiff (PAS) technic. In addition some specimens were stained with crystal violet, by Gomori's reticulin method, by the Masson stain, and by Verhoeff's technic for elastica.

Twenty-five hearts with mitral stenosis were collected from the autopsy files of this hospital. Eight of the patients had died within 2 weeks of mitral valvotomy at which the atrial appendages had been obtained. The appendages of the other 17 hearts were examined in a similar manner. From each heart a left ventricular block was taken as recommended by Gross, Antopol, and Sacks.[5]

As controls the left atrial appendages from 20 necropsies were examined. These were selected so that the average age of this group was similar to that of the patients operated upon for mitral stenosis. Cases of myocarditis or pericarditis were excluded.

Results

Anatomic Observations

Aschoff bodies are very variable in appearance and therefore difficult to define. In this investigation the criteria of Gross and Ehrlich[6] have been applied as far as possible. Some Aschoff cells have nuclei resembling those of the Anitschkow myocyte. Others have vesicular nuclei with prominent nucleoli. The cytoplasm is generally basophilic. An Aschoff node is formed by round or oval collections of these cells, some of which are usually multinucleated. The great majority of Aschoff bodies in this investigation were embedded in altered collagen and resembled the "mosaic" variety of Gross and Ehrlich and also the "banded" type described by MacCallum[7] as characteristic of rheumatic activity in the left atrium (fig. 1). Gross and Ehrlich's "coronal" Aschoff body was seen less fre-

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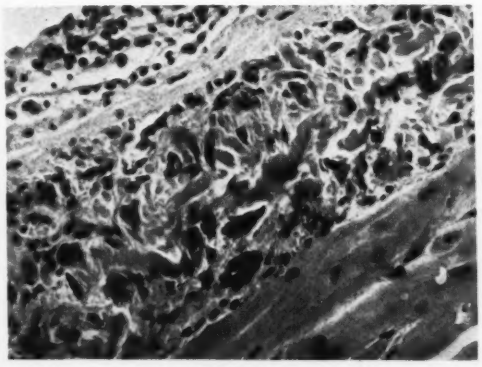

Figure 1

Part of large "mosaic" type Aschoff body in subendocardium. The endocardium is at the upper left. Hematoxylin and eosin stain.

quently (fig. 2). Polarization and fibrillar change were rare. The majority of these lesions were situated in the loosely constructed subendocardial tissue but endocardial lesions were also frequent.

Foci of inflammatory cells in the endocardium and subendocardium that did not fulfill the criteria for Aschoff bodies were considered to be "nonspecific granulomas" (fig. 3). Generally they differed from typical Aschoff nodes by the absence of characteristic nuclei. Specimens with clusters of inflammatory cells related to organized thrombi were not included in this group.

Swelling, eosinophilia, or necrosis of collagen was almost invariable in the proximity of Aschoff cells and of nonspecific granulomas. Even in appendages without foci of inflammatory cells a few small areas of damaged connective tissue could usually be found, and sometimes extensive areas of such change were present. Although none of this material stained like fibrin by the PTAH method, it fulfilled the criteria for "fibrinoid."[8] It was PAS positive and stained metachromatically with crystal violet. Only some of this material was metachromatic by the toluidine blue method. This stain did, however, show widespread metachromasia surrounding Aschoff bodies and also elsewhere in the endocardium, particularly in its most superficial layer.

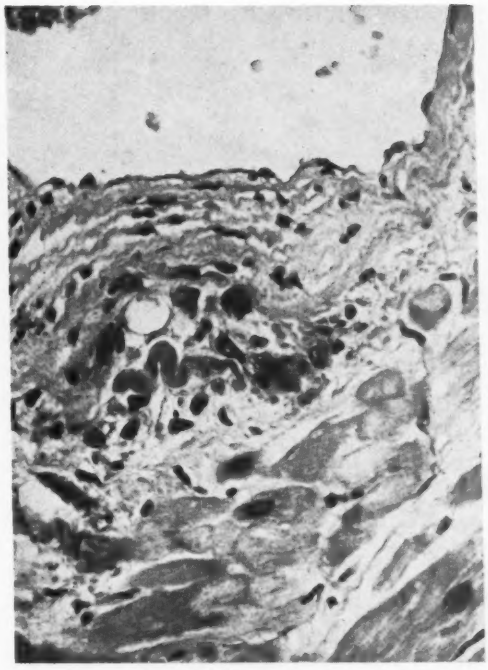

Figure 2

"Coronal" type subendocardial Aschoff body. Hematoxylin and eosin stain.

Appendages obtained at valvotomy were divided into three groups: those with Aschoff bodies, those with nonspecific granulomas, and those without either lesion. The task of separating Aschoff bodies from nonspecific granulomas was difficult. A determined effort was made to use the same criteria for this distinction throughout the investigation. Marked variation in the frequency of Aschoff bodies was observed in different blocks from the same specimen. On this account and because of the variable amount of tissue received from different patients an assessment of the frequency of Aschoff bodies in the positive specimens was not attempted. The transition from "early" to "senescent"[6] Aschoff bodies was so gradual that subdivision into such categories seemed impracticable.

Of 316 biopsies, 130 (41 per cent) were positive for Aschoff bodies and 72 (23 per cent) showed nonspecific granulomas. The average age of patients with Aschoff bodies

Table 1

Average Age of Patients with Aschoff Bodies, Nonspecific Granulomas, and without Either Lesion (Total 291 Cases)

	121 Patients with Aschoff bodies	66 Patients with nonspecific granulomas	104 Patients with neither
Mean age (years) and standard deviation (S. D.)	33.0 ± 8.2	37.0 ± 7.6	40.6 ± 9.4

Table 2

Relationship between Aschoff Bodies, Atrial Fibrillation, and Organized Thrombi (Total 256 cases)

	Fibrillation		Regular rhythm	
	Thrombi	No thrombi	Thrombi	No thrombi
No. of patients	53	49	10	144
Patients with Aschoff bodies	3 (6%)	23 (47%)	6 (60%)	86 (60%)

was 4 years less than that of those with nonspecific granulomas and more than 7 years less than that of patients without any inflammatory foci in the endocardium (table 1). The differences between these means were statistically significant, since they amounted to considerably more than twice their standard errors.

Organized endocardial thrombi consisting of vascularized fibrous tissue with occasional hemosiderin deposits (fig. 4) were seen in more than a quarter of all specimens (76). Collections of inflammatory cells, mostly lymphocytes and plasma cells with occasional foreign-body giant cells (fig. 5), were often seen near these areas of organization. Table 2 shows that Aschoff bodies were rare (9 of 63 or 13 per cent) in patients with atrial thrombosis. Most of these (53 of 63 or 84 per cent) also had atrial fibrillation. Patients with fibrillation were subdivided into two groups. Of those with fibrillation but without thrombosis 47 per cent (23 of 49) had Aschoff bodies in their biopsy compared with only 6 per cent (3 of 53) of those with both thrombosis and fibrillation. The difference between these groups is statistically highly significant ($\chi^2 = 22.6$; $p<0.001$). Therefore thrombosis and not fibrillation is the principal factor associated with a lowered incidence of Aschoff bodies. Among patients with regular rhythm only 10 had organized thrombi, too few for statistical evaluation.

Enlargement of cardiac muscle fibers and interstitial myocardial fibrosis were frequent but variable. Binucleate cardiac muscle fibers were common and occasional fibers with more nuclei could be found (fig. 6). Myocardial hypertrophy was particularly striking in specimens with organized thrombi. Mitotic figures were not seen in any muscle fibers and the shape of some of these hypertrophied nuclei was so irregular that it suggested the possibility of amitotic division. No Aschoff bodies were observed that could be interpreted as indubitably myocardial in location. The atrial appendage has such a convoluted structure that lesions that are apparently embedded in the atrial wall may actually be quite close to a pocket of endocardium.

The pericardial and subpericardial tissues contained no Aschoff bodies. Foci of lymphocytes and fibrosis were, however, seen in most specimens. Table 3 shows that in 108 of the 316 appendages the pericardial lining had undergone metaplasia and resembled cuboidal or even columnar epithelium (fig. 7). Forty-seven per cent of the specimens with this pericardial "cubing" also showed endocardial or subendocardial Aschoff bodies compared with 37 per cent of the appendages without pericardial cubing. This difference is

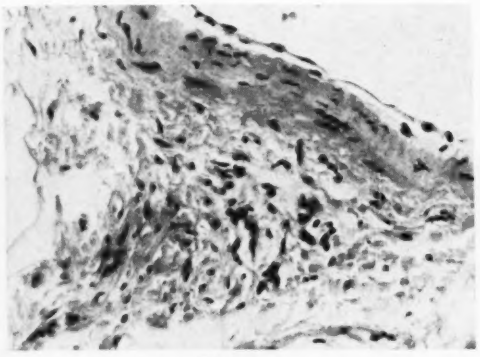

Figure 3

"Nonspecific" subendocardial granuloma. Hematoxylin and eosin stain.

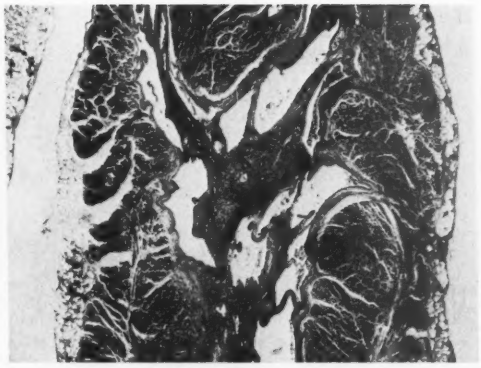

Figure 4

Organized endocardial thrombus, left atrium. Hematoxylin and cosin stain.

statistically not significant ($\chi^2 = 2.5$ $p>0.1$). Rather surprisingly, cubing was also seen in 40 per cent (8 of 20) of control necropsies on patients without any evidence of rheumatic disease. Cubing therefore appears to be an entirely nonspecific change, as was found previously by Enticknap.[9]

Autopsy material was available from eight patients who died within 2 weeks of mitral valvotomy and from 16 patients who had not been operated upon. Since the average age of both groups was similar, they were considered together. In 22 of 24 cases the ventricular myocardium and the atrial appendage presented similar findings. In this autopsy series 33 per cent of patients (8 of 24) showed rheumatic activity in the left atrial appendage. This is slightly lower than the 41 per cent recorded in the biopsy series. The average age of both series was almost identical, and it seems probable that there was no significant difference in the severity of the rheumatic process in the autopsy and biopsy series. Presumably other factors such as valvular and myocardial scarring were principally responsible for the fatal outcome in patients coming to autopsy.

Erythrocyte Sedimentation Rates and Aschoff Bodies

A sedimentation rate above 10 mm. per hour was recorded as often in patients with Aschoff bodies as in those with negative biopsies. Values of 30 mm. or more were seen more frequently in patients with Aschoff bodies but numbers were too small for statistical evaluation. It is therefore concluded that in patients with mitral stenosis a moderate elevation of the sedimentation rate did not necessarily indicate rheumatic activity. Preoperative values above 30 mm., however, may suggest a greater likelihood of finding Aschoff bodies.

Aschoff Bodies in the Two Sexes

Age and sex were known in 295 patients of the total of 316. Table 4 shows that the number of female patients in this group was more than twice the number of males. Nevertheless, the percentage of biopsies with Aschoff bodies was almost identical in the two sexes. The incidence of nonspecific granulomas was also not significantly different in the two sexes ($\chi^2 = 0.6$; $p>0.3$).

Relationship of Aschoff Bodies to Age

The percentage of Aschoff bodies was highest in the youngest patients. It fell from 66 per cent in those aged 15 to 20 years to 14 per cent in patients over 55 years (fig. 8). Of 178 patients aged 40 years or less, 52 per cent had appendages with Aschoff bodies. Only 27 per cent of 117 patients aged more than 40 years had positive biopsies. This difference was statistically highly significant ($\chi^2 = 18.7$; $p<0.01$). It diminished, but did not disappear, if patients with organized thrombi were excluded.

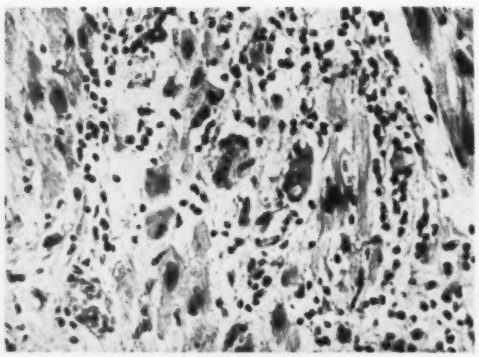

Figure 5

Chronic inflammatory reaction with giant cells of foreign-body type in atrium with organized thrombus. Hematoxylin and eosin stain.

Figure 6

Hyperplasia of cardiac muscle in specimen with organized thrombus. A binucleate muscle fiber is seen in the center. Hematoxylin and eosin stain.

Annual Incidence of Aschoff Bodies

The 316 atrial appendages on which this study is based were obtained during the years 1949 to 1959. During this period, the percentage of positive reports tended to diminish (fig. 9). The greatest drop occurred between 1951 (52 per cent) and 1952 (34 per cent). This fall, however, was statistically not significant ($\chi^2 = 0.9$; $p > 0.3$).

Seasonal Changes in Aschoff Bodies

Seasonal changes in the incidence of Aschoff bodies were also investigated (table 5). The proportion of positive biopsies was lowest in June (25 per cent) and maximal in September (65 per cent). The differences between the four quarters were statistically highly significant ($\chi^2 = 13.9$; $p < 0.01$). Fibrinoid change of the cardiac connective tissue showed a similar seasonal fluctuation but this did not reach statistical significance.

Discussion

The percentage of Aschoff bodies found by previous authors in atrial appendages obtained at mitral valvotomy has varied from 74[10] to 19 per cent.[11] The mean percentage of biopsies with Aschoff bodies in 3,347 specimens examined by 39 previous authors was 39.2 per cent.[1, 4, 9–44] This figure is very similar to 41 per cent, the frequency of positive biopsies in this investigation, which dealt with 316 patients.

The extreme variation in the results reported by different authors requires explanation. Chiari[29] suggested that geographic variation of the disease might be responsible. This seems unlikely because the two groups of investigators reporting the highest and the lowest percentage of Aschoff bodies both work in the same part of the United States of America. Krymski[40] attributed the high frequency of Aschoff bodies in his series to the examination of many sections from each specimen. This may be a factor, but Sabiston and Follis,[10] whose percentage was even higher, examined only one section per block. It therefore does not seem likely that examination of different numbers of sections per block will account for the variation.

The disagreements among previous authors are almost certainly due to differences in morphologic criteria for the Aschoff body.[4, 45, 46] Some considered fibrinoid degeneration to be the earliest precursor of an Aschoff body rather than a nonspecific lesion.[4] Their percentage of positive biopsies was therefore high. Others employed much stricter criteria.[45] Tedeschi, Wagner, and Pani[11] divided atrial Aschoff bodies into "active" and "quiescent" lesions. They insisted on myofibril damage, connective-tissue alterations, and a surrounding inflammatory reaction before considering an Aschoff body to be "active." In the present investigation, connective-tissue

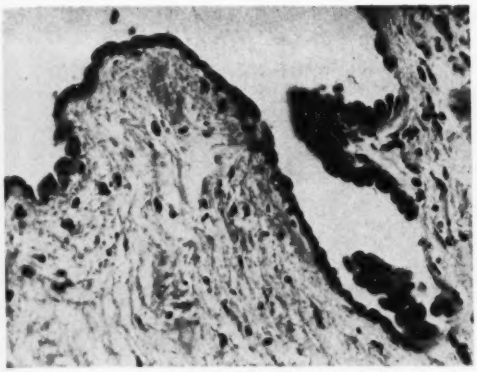

Figure 7

Pericardial metaplasia ("cubing"). Hematoxylin and eosin stain.

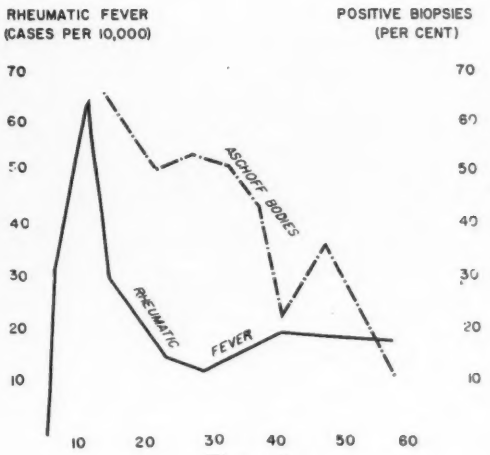

Figure 8

Variations with age of the percentage of atrial appendages positive for Aschoff bodies and of the incidence of rheumatic fever in the U.S.A.

changes and an inflammatory reaction were found almost invariably in the presence of Aschoff bodies. Myocardial damage depended on the proximity of the Aschoff body to the atrial myocardium and not on the freshness of the lesion. The histologic criteria of Tedeschi, Wagner, and Pani[11] for "activity" were therefore found to be inapplicable. Moreover there was little evidence that their patients with "active" lesions differed clinically from those with "quiescent" Aschoff bodies. It must be admitted that the definition of an Aschoff body remains subjective. The similarity of the percentage of Aschoff bodies in this investigation (41 per cent) to the mean of all the previously reported series (39 per cent) does, however, suggest that the criteria adopted here resemble those of most previous investigators.

In order to assess the significance of Aschoff bodies in the atrial appendage removed at mitral valvotomy it is clearly important to determine whether lesions in the atrial appendage indicate similar lesions in the rest of the heart. A few authors have expressed some doubts about this correlation.[19, 20] Study of material from 24 autopsies in this department and review of the literatures[4, 20, 22, 23, 40, 51, 52] show that Aschoff bodies in the atrial appendage are usually accompanied by evidence of rheumatic activity in the rest of the heart. Absence of atrial lesions does not necessarily imply absence of Aschoff bodies from the ventricle.

Aschoff cells are generally considered to be of connective-tissue origin.[11, 24, 47, 48] Nevertheless Murphy[49] recently reaffirmed his belief that Aschoff cells originate from cardiac muscle or even from smooth muscle of the endocardium. In this investigation Aschoff nodes were never found in the atrial myocardium. Hypertrophic cardiac muscle fibers, however, with two or even more nuclei were frequently seen, particularly in biopsies with organized thrombi. These specimens had a strikingly low incidence of Aschoff bodies (table 2). Moreover, Aschoff cells could easily be distinguished from other cardiac giant cells such as hypertrophic muscle fibers (fig. 6) and giant cells of foreign-body type (fig. 5).[11, 50] We therefore agree with the majority of previous investigators who considered the Aschoff cell to be the response of the cardiac connective tissue to rheumatism.

The significance of endocardial inflammatory lesions that do not fulfill the criteria for Aschoff bodies has been widely debated.[9, 32, 45] With the exception of Saphir[45] most of these authors considered that such lesions probably indicate some rheumatic activity. Patients with such lesions ("nonspecific granulomas"

Table 3

Frequency of Aschoff Bodies in Patients with and without Pericardial "Cubing"

	Specimens with cubing	Specimens without cubing	Total no. specimens
No. of patients	108	208	316
Patients with Aschoff bodies	51 (47%)	79 (37%)	130 (41%)

Table 4

Biopsy Observations in Male and Female Patients (295 Cases)

	No.	Mean age (yrs.) and S. D.	No. with Aschoff bodies	No. with non-spec. granulomas	No. without either lesion
Males	84	36.6 ± 9.3	35 (41.5%)	21 (25.0%)	28 (33.5%)
Females	211	37.5 ± 8.2	90 (42.5%)	44 (20.8%)	77 (36.7%)
Total	295	37.2 ± 8.5	125 (42.2%)	65 (22.0%)	105 (35.8%)

in this series, figure 3) were intermediate in age between patients with Aschoff bodies and subjects without any inflammatory endocardial foci (table 1). There seem to be two possible explanations for this result. Either older subjects react less specifically to rheumatism or nonspecific granulomas include both rheumatic lesions no longer histologically typical and also inflammatory foci of unknown origin. After exclusion of patients with organized thrombi the age difference between subjects with nonspecific granulomas and those without inflammatory foci diminished strikingly. We are therefore in favor of the second explanation, namely that the group of nonspecific granulomas is not homogeneous and contains some rheumatic lesions and others of unknown origin.

The relationship between mural thrombosis and the degree of rheumatic activity has been discussed by many previous investigators. De la Chapelle, Graef, and Rottino[50] found thrombosis more frequently in active carditis. Tedeschi, Wagner, and Pani[11] could find no correlation between thrombi and Aschoff bodies in the atrial appendage. Most previous authors, however, have only rarely seen Aschoff bodies in biopsies from patients with atrial thrombosis.[4, 17, 20, 30, 36, 38] We are in agreement with these investigators. Rheumatic activity is well known to diminish with increasing age. The average age of our patients with organized thrombi was slightly higher than that of the series as a whole (41.5 compared to 37 years). Nevertheless, the low incidence of Aschoff bodies in the presence of thrombi remains highly significant. Most patients with atrial thrombosis also have fibrillation. Previous authors have been unable to determine whether the decreased incidence of Aschoff bodies in these patients is due to the thrombosis per se or to the fibrillation.[3, 4] Analysis of our results shows the Aschoff bodies are significantly less frequent in biopsies from patients with both fibrillation and organized thrombi than in those with fibrillation but without thrombi. We therefore conclude that thrombosis, rather than fibrillation, is the principal factor associated with a lowered incidence of Aschoff bodies in the atrial appendage. Presumably patients in this group form a significant proportion of those who show no rheumatic lesions in the appendage but have Aschoff bodies in the rest of the heart. The results of this study therefore agree with previous work indicating that fibrillation alone produces no histologic changes.[53] McGoon and Henly[54] in an autopsy study found that atrial thrombosis did not affect rheumatic activity in the ventricular myocardium. It therefore seems that thrombosis may protect the appendage by a local effect. Mechanical factors thus appear to be important in determining the site of Aschoff bodies. It seems very likely that the preferential localization of rheumatic lesions in certain parts of the heart[55] is also largely determined by mechanical forces.

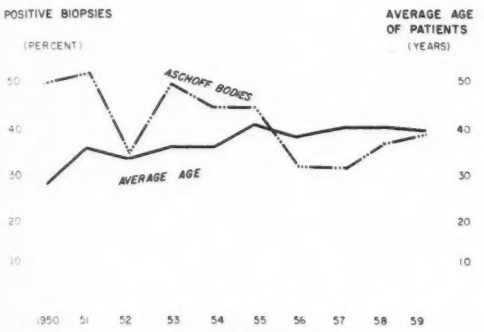

Figure 9

Annual variation in the percentage of positive biopsies for Aschoff bodies compared with the average age of patients operated upon.

Figure 10

Seasonal changes in the percentage of biopsies positive for Aschoff bodies compared with the incidence of rheumatic fever in Baltimore 1956 -1959.

Previous attempts to correlate the presence of Aschoff bodies with clinical activity in mitral valvotomy patients have produced contradictory results. Some[10, 11, 14, 17, 32, 41] considered there was some correlation between rheumatic activity and laboratory tests. Others[1, 3, 22, 26, 42] could not confirm these claims. The most popular test for rheumatic activity has been the erythrocyte sedimentation rate. The antistreptolysin titer and C-reactive protein test were also performed in some investigations. Our results agree with those who found that an elevated erythrocyte sedimentation rate is no more frequent in patients with Aschoff bodies than in those without histologic activity. From a study of the literature it seems probable that other laboratory tests presently available are not much more successful. Since absence of clinical activity is one of the criteria that must generally be fulfilled before patients are considered for operation, the failure of attempts to correlate clinical and histologic activity is perhaps not surprising.

The discrepancy between clinical and histologic features has been explained by questioning the significance of these biopsy lesions.[9] Since our observations and those of others [4, 20, 22, 23, 40, 51, 52] agree that such Aschoff bodies generally indicate a widespread rheumatic carditis, this explanation cannot be valid. Antibiotic and steroid prophylaxis has been considered responsible for the lack of correlation between clinical and histologic findings.[11] Only 43 of our patients were known to have had penicillin or sulfonamide and 42 per cent of these had positive biopsies. Penicillin and sulfonamide were thus frequently unable to suppress histologic evidence of rheumatism. Only 10 patients were receiving salicylates or adrenal steroids. Clearly the lack of correlation between clinical state and histologic features cannot be explained by prophylaxis. Lannigan[4] came to similar conclusions. Some patients received chemotherapy because of suspected clinical activity. In addition the duration of administration was often inadequate. It seems possible, nevertheless, that prevention of recurrent rheumatic fever by penicillin or sulfonamide is less effective histologically than it appears to be clinically. Cortisone or salicylates may produce better results but the number of patients in this series (10) was too small for statistical evaluation.

The morbidity due to rheumatic fever in this country is impossible to determine. Ac-

Table 5

Changes in the Proportion of Positive Biopsies Obtained at Valvotomies Performed in Different Months (316 Patients)

Month	Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
No. of cases	37	40	30	27	20	28	24	13	20	37	25	15	316
With Aschoff bodies	18	16	13	9	6	7	13	6	13	13	11	5	130
	49%	40%	43%	33%	30%	25%	54%	46%	65%	35%	44%	33%	41%

cording to the Vital Statistics Reports of the U.S.A. for 1958 the mortality for both sexes is identical (0.5 per 100,000). This suggests that morbidity of acute rheumatic fever also may not greatly differ in the two sexes. The number of female patients with mitral stenosis in this series, as in other reports, was more than twice the number of males (table 4). Nevertheless, the incidence of positive biopsies was almost identical in both sexes (42.5 per cent and 41.5 per cent). In the only large series analyzed previously for sex incidence a somewhat higher percentage of positive biopsies was found in female patients.[3] The similarity in the proportion of positive biopsies in this study suggests that histologic rheumatic activity in patients with mitral stenosis, like the incidence of rheumatic fever in the general population, is equal in the two sexes.

The frequency of positive biopsies diminished strikingly with increasing age. Previous investigators have observed this inverse relationship.[3, 11] Figure 8 shows the variation with age of the percentage of positive biopsies in this series and of the incidence of acute rheumatic fever in the United States.[56] A comparison of the two curves suggests that histologic rheumatic activity, while diminishing with advancing age, often persists for 20 to 30 years after the disease has become clinically quiescent. This conclusion, based on epidemiologic data, is similar to that reached by Biörck et al.[17] after studying the case histories of patients submitted to valvotomy.

During the period covered by this investigation, the percentage of positive biopsies fell slightly (fig. 9). During the same period, the indications for mitral valvotomy were widened. Older patients were operated upon and a history of peripheral embolism was no longer considered a contraindication. The average age of patients submitted to the operation therefore rose from 26.5 to 38.5 years. This rise in average age and the increase in atrial thrombosis are probably sufficient to account for the fall in the percentage of positive biopsies. There thus seems to have been no significant change in the percentage of positive biopsies during the past 10 years. While there has been a considerable fall in the mortality from acute rheumatic fever, the number of patients admitted to this hospital with the disease fell only slightly—from 46 in 1950 to 35 in 1958. If it is accepted that these Baltimore figures reflect the incidence of acute rheumatic fever in the U.S.A., then it becomes probable that the marked fall in mortality has not been accompanied by a corresponding decrease in the incidence of the disease.

Investigation of seasonal changes in the percentage of positive biopsies (table 5) showed that the proportion of positive biopsies was lowest in June (29 per cent) and maximal in September (65 per cent). The mean age of patients operated upon did not change significantly from month to month. This seasonal variation in the percentage of Aschoff bodies suggests that in patients submitted to mitral valvotomy the rheumatic process is intermittently active in spite of the absence of clinical signs. Previous authors[3, 32] found no seasonal trend. Their series were, however, smaller, and the study of McNeely, et al.[3] was based on observations at two hospitals where histologic criteria may have differed. Acute rheu-

matic fever is well known to have a seasonal incidence. In this investigation the admission dates of 193 patients admitted for acute rheumatic fever to several Baltimore hospitals during 1956 to 1959 were used to estimate the seasonal incidence of the disease. As in a previous report[57] the greatest number of patients with acute rheumatic fever was admitted to the hospital during April. The month with the highest percentage of positive biopsies thus lags approximately 5 months behind the maximum incidence of the onset of the disease (fig. 10). This interval of 5 months appears to represent the average age of Aschoff bodies in the atrial appendage of our valvotomy patients. Gross and Ehrlich[6] and McKeown[58] estimated, by clinicopathologic correlation, the total life span of an Aschoff body to be 6 to 9 months. The conclusion that the Aschoff bodies dealt with in this investigation have a mean age of 5 months is thus consistent with previous work.

It is concluded that rheumatic activity continues in many patients with mitral stenosis long after presently available laboratory tests have become negative. In addition, we have shown that the histologic process in such patients undergoes seasonal exacerbations. We consider that these results establish the concept of a "subclinical" rheumatic process, which has been postulated by many previous investigators.

Summary

Three hundred and sixteen biopsies of atrial appendages obtained at mitral valvotomy were studied histologically. They were divided into those with Aschoff bodies (41 per cent), those with nonspecific granulomas (23 per cent), and those without either lesion. These findings were compared with those of previous investigators.

A study of 24 hearts with mitral stenosis and survey of the literature showed that Aschoff bodies in the left atrial appendage are usually accompanied by similar lesions in the rest of the heart.

The average age of patients with Aschoff bodies in their atrial biopsy was 4 years less than that of those with "nonspecific granulomas" and more than 7 years less than that of patients without inflammatory foci in the endocardium. The etiology of "nonspecific granulomas" is discussed.

Aschoff bodies were rare in patients with organized atrial thrombi, most of whom were fibrillating. Statistical analysis showed that thrombosis rather than fibrillation was the principal factor associated with a lowered incidence of Aschoff bodies. It was concluded that mechanical factors may determine the localization of rheumatic lesions in the heart.

Elevated sedimentation rates were recorded as often in patients with negative biopsies as in those with Aschoff bodies.

The percentage of positive biopsies fell from 66 per cent in patients aged 15 to 20 years to 14 per cent in patients aged over 55 years. The age incidence of Aschoff bodies has been compared with that of acute rheumatic fever, which is rare after the age of 15 years. It is concluded that in patients with mitral stenosis, histologic activity may continue for 20 years or more in the absence of clinical signs and symptoms.

The proportion of positive biopsies was lowest in June and maximal in September. This seasonal change suggests that the histologic process is only intermittently active. The seasonal variation in the percentage of Aschoff bodies is discussed in relation to the seasonal incidence of acute rheumatic fever.

Our results appear to establish the concept of a "subclinical" rheumatic process which has been postulated by many previous investigators.

References

1. Pinniger, J. L.: The left auricular appendage in mitral stenosis. A study of 15 cases submitted to valvotomy. St. Thomas's Hosp. Reports **7**: 54, 1951.
2. Smyth, C. J., Bunim, J. J., Clark, W. S., Crain, D. C., Demartini, F. E., Duff, I. F., Engleman, E. P., Graham, D. C., Montgomery, M. M., Norcross, B. M., Polley, H. F., Ropes, M. W., and Rosenberg, E. F.: Rheumatism and arthritis. Review of American and English literature of recent years (Twelfth Rheumatism Review) Part I. Ann. Int. Med. **50**: 366, 1959.
3. McNeely, W. F., Ellis, L. B., and Harken,

D. E.: Rheumatic "activity" as judged by the presence of Aschoff bodies in auricular appendages of patients with mitral stenosis. II. Clinical aspects. Circulation **8**: 337, 1953.

4. Lannigan, R.: The rheumatic process in the left auricular appendage. J. Path. & Bact. **77**: 49, 1959.
5. Gross, L., Antopol, W., and Sacks, B.: A standardized procedure suggested for microscopic studies on the heart. Arch. Path. **10**: 840, 1930.
6. Gross, L., and Ehrlich, J. C.: Studies on the myocardial Aschoff body. I. Descriptive classification of lesions. Am. J. Path. **10**: 467, 1934.
7. MacCallum, W. G.: Rheumatic lesions of the left auricle of the heart. Bull. Johns Hopkins Hosp. **35**: 329, 1924.
8. Altshuler, C. H., and Angevine, D. M.: Histochemical studies on the pathogenesis of fibrinoid. Am. J. Path. **25**: 1061, 1949.
9. Enticknap, J. B.: Biopsy of the left auricle in mitral stenosis. Brit. Heart J. **15**: 37, 1953.
10. Sabiston, D. C., and Follis, R. H.: Lesions in auricular appendages removed at operations for mitral stenosis of presumed rheumatic origin. Bull. Johns Hopkins Hosp. **91**: 178, 1952.
11. Tedeschi, C. G., Wagner, B. M., and Pani, K. C.: Studies in rheumatic fever. 1. The clinical significance of the Aschoff body based on morphologic observations. Arch. Path. **60**: 408, 1955.
12. Janton, O. H., Glover, R. P., O'Neill, T. J. E., Gregory, J. E., and Froio, G. F.: Results of the surgical treatment for mitral stenosis. Analysis of one hundred consecutive cases. Circulation **6**: 321, 1952.
13. Waaler, E.: Activity of the rheumatic auriculitis in chronic valvular disease. The distribution of rheumatic auriculitis. Acta path. microb. scandinav., Suppl. **93**: 211, 1952.
14. Kuschner, M., Ferrer, I., Harvey, R. M., and Wylie, R. H.: Rheumatic carditis in surgically removed auricular appendages. Am. Heart J. **43**: 286, 1952.
15. Catto, M., Smith, G., and Taylor, W. A.: Rheumatic lesions in surgically removed auricles. J. Path. & Bact. **64**: 673, 1952.
16. Bailey, C. P., Bolton, H. E., and Redondo-Ramirez: Surgery of the mitral valve. Surg. Clin. North America **32**: 1807, 1952.
17. Biorck, G., Winblad, S., and Wulff, H. B.: Studies in mitral stenosis. II. Observations on incidence of active rheumatic carditis in left auricular appendages resected at operation for mitral stenosis. Am. Heart J. **44**: 325, 1952.
18. Magri, G., Angelino, P. F., Actis Dato, A., and Levi, V.: Reperti istologici nelle auricole amputate in corso di valvutomia mitralica. Minerva med. **44**: 1763, 1953.
19. Andrus, E. C., Blalock, A., and Milnor, W. R.: Surgical treatment of mitral stenosis. Arch. Surg. **67**: 790, 1953.
20. Decker, J. P., Hawn, C. Van Z., and Robbins, S. L.: Rheumatic "activity" as judged by the presence of Aschoff bodies in auricular appendages of patients with mitral stenosis. I. Anatomic aspects. Circulation **8**: 161, 1953.
21. Soloff, L. A., Zatuchni, J., Janton, O. H., O'Neill, T. J. E., and Glover, R. P.: Reactivation of rheumatic fever following mitral commissurotomy. Circulation **8**: 481, 1953.
22. McKeown, F.: The left auricular appendage in mitral stenosis. Brit. Heart J. **15**: 433, 1953.
23. Thomas, W. A., Averill, J. H., Castleman, B., and Bland, E. F.: The significance of Aschoff bodies in the left atrial appendage. A comparison of 40 biopsies removed during mitral commissurotomy from 40 patients dying with fulminating rheumatic fever. New England J. Med. **249**: 761, 1953.
24. Meessen, H.: Aschoffsche Knötchen in chirurgisch gewonnen Herzohren. Zentralbl. Path. **90**: 403, 1953.
25. Luse, S. A., Rusted, I. E., and Edwards, J. E.: Aschoff bodies in surgically resected auricular appendages and elsewhere in the heart in mitral stenosis. Lab. Invest. **3**: 483, 1954.
26. Denst, J., Edwards, A., Neuburger, K. T., and Blount, S. G.: Biopsies of the lung and atrial appendages in mitral stenosis. Correlation of data from cardiac catheterization with pulmonary vascular lesions. Am. Heart. J. **48**: 506, 1954.
27. Elster, S. K., Wood, H. F., and Seely, R. D.: Clinical and laboratory manifestations of the post commissurotomy syndrome. Am. J. Med. **17**: 826, 1954.
28. Fojanini, G., Di Matteo, G., and Conti, A.: Aspetti istologici delle auricole asportate nei patienti sottoposti a commissurotomia mitralica. Arch. ital. chir. **79**: 121, 1955.
29. Chiari, H.: Mikroskopische Befunde in der Wand des linken Herzohres bei wegen Mitralstenose Valvulotomierten. Wien. klin. Wchnschr. **67**: 309, 1955.
30. Tragerman, L. J., and Corley, L. C.: Rheumatic lesions in left atrial appendages. Pathologic studies of material removed during mitral commissurotomy. California Med. **82**: 163, 1955.
31. Gil, J. R., Rodriguez, H., and Ibarra, J. J.: Incidence of asymptomatic active rheumatic cardiac lesions in patients submitted to mitral commissurotomy and the effect of cortisone on these lesions. Am. Heart J. **50**: 912, 1955.

32. MANCHESTER, B., SCOTTI, T. M., REYNOLDS, M., AND DAWSON, W. H.: Aschoff bodies in left auricular appendages of patients with mitral stenosis. Clinicopathologic study, including post operative follow-up. Arch. Int. Med. 95: 231, 1955.

33. CHAVEZ, I., VAQUERO, M., AND MENDOZA, F.: Etude de 100 malades souffrant de sténose mitrale soumis à la commissurotomie et préalablement cathéterisés. Acta cardiol. 10: 209, 1955.

34. CLARK, R. M., AND ANDERSON, W.: Rheumatic activity in auricular appendages removed at mitral valvoplasty. Am. J. Path. 31: 809, 1955.

35. HERMANN, L. M., DIMITROFF, S. P., COSBY, R. S., AND GRIFFITH, G. C.: The results of mitral commissurotomy one to three years after surgery. Dis. Chest 30: 20, 1956.

36. MARTIN, J. F., FROMENT, R., PERRIN, A., AND BRANC, J.: Confrontation anatomoclinique à partir de 50 biopsies auriculaires chez des mitraux opérés. Arch. mal. coeur 49: 134, 1956.

37. VAN BOGAERT, A., AND FANNES, E.: Réactivation post opératoire de la maladie rheumatismale. Acta cardiol. 11: 141, 1956.

38. PROVENZALE, L., AND TONELLI, L.: Il problema dell attività reumatica nei mitralici candidati all intervento. Arch. Chir. Tor. 13: 89, 1956.

39. KOCHSIEK, K.: Zur normalen und pathologischen Morphologie der Heszohren. Frankfurt Ztschr. Path. 68: 287, 1957.

40. KRYMSKY, L. D.: Ninety three examinations of the left auricular appendage of the heart in mitral stenosis. Ztschr. ärztl. Fortbild. 52: 541, 1958.

41. BRUSCA, A., BRUZZONE, P. L., AND TORCHIANA, B.: Frequenza dei noduli di Aschoff nelle auricole dei mitralici in rapporto ai valori della Proteina C reattiva e del titolo antistreptolisinico O del siero. Minerva med. 49: 1284, 1958.

42. HARTLEB, O., MICHEL, D., AND HERBST, M.: Zur Bedeutung der Aschoffschen Knötchen als Aktivitätskriterium bei Mitralstenosen. Klin. Wchnschr. 36: 203, 1958.

43. KUPRIANOV, P. A.: Una cardite reumatica a lento decorso deve considerarsi come una contraindicazione all operazione di commissurotomia mitralica? Minerva cardioangiol. 7: 64, 1959.

44. STEWART, H. J., AND GLENN, F.: Mitral Valvulotomy. Springfield, Illinois, Charles C Thomas, Publisher, 1959.

45. SAPHIR, O.: The Aschoff Nodule. Am. J. Clin. Path. 31: 534, 1959.

46. WAGNER, B. M.: Letter. Lancet 1: 1205, 1959.

47. RUEBNER, B.: The relationship between muscle damage and the Aschoff cell in rheumatic carditis. J. Path & Bact. 68: 101, 1954.

48. GOULD, S. E., Editor: Pathology of the Heart. Springfield, Illinois, Charles C Thomas, Publisher, 1960, p. 1080.

49. MURPHY, G. E.: On muscle cells, Aschoff bodies and cardiac failure in rheumatic heart disease. Bull. New York Acad. Med. 35: 619, 1959.

50. DE LA CHAPELLE, C. E., GRAEF, I., AND ROTTINO, A.: Studies in rheumatic heart disease. Analysis of 119 hearts wtih special reference to the relationship of auricular fibrillation to mitral valvular deformity and certain rheumatic tissue changes. Am. Heart J. 10: 62, 1934.

51. KUSCHNER, M., AND LEVIEFF, L.: Correlation between active rheumatic lesions in the left auricular appendage and elsewhere in the heart. Am. J. M. Sc. 226: 290, 1953.

52. CASTELLANOS, A., SALAS PANISELLO, CALVINO, J. M., AND BLAIR, J. D.: Alteraciones post mortem de la oregula izquierda en 14 casos de fiiebre reumatica aguda con especial referencia a los cuerpos de Aschoff. Rev. cubana cardiol. 15: 263, 1954.

53. KLETSKY, S.: Microscopic lesions in the left atrial endocardium in chronic rheumatic heart disease. Am. Heart. J. 29: 739, 1945.

54. MCGOON, D. C., AND HENLEY, W. S.: The significance of auricular fibrillation and auricular thrombosis in mitral valve surgery. Bull. Johns Hopkins Hosp. 91: 419, 1952.

55. GROSS, L., AND EHRLICH, J. C.: Studies on the myocardial Aschoff body. II. Life cycle, sites of predilection and relation to clinical course of rheumatic fever. Am. J. Path. 10: 489, 1934.

56. Sickness experience in selected areas of the United States. U. S. Public Health Monograph No. 25, Washington, 1955, p. 13.

57. PAUL, J. R.: Clinical Epidemiology. Chicago, University of Chicago Press, 1958, p. 183.

58. MCKEOWN, F.: The pathology of rheumatic fever. Ulster. M. J. 14: 97, 1945.

59. WAGNER, B. M., AND TEDESCHI, C. G.: Studies in rheumatic fever, II. Origin of cardiac giant cells. Arch. Path. 60: 423, 1955.

Sodium from Drinking Water as an Unsuspected Cause of Cardiac Decompensation

By GEORGE B. ELLIOTT, M.B., AND ELIZABETH A. ALEXANDER, R.T.

LARGE AMOUNTS of sodium may exist unsuspected in tasteless form in ordinary drinking water. This forms a source of perplexing decompensation in well-controlled heart disease and a danger for patients who believe they are following safe low-sodium diets.

This information is likely to be of clinical importance over the whole midwest of North America, where soils are often derived from underlying marine formations of six successive ancient sea beds. Water from private wells that fill by lateral seepage through soils are often high in sodium content. Much of this sodium is in the form of sulfate or nitrate and more difficult to recognize by taste than chloride. Unlike the surrounding prairies the water supply for the city of Calgary has a low sodium content, for it is essentially surface rain run-off in a river from the Rocky Mountains.

We wish to record two illustrative instances in which recurrent episodes of cardiac failure at home ceased after substitution of a low- for an unsuspected high-sodium water supply. Both patients recovered in the hospital in Calgary even when their therapeutic, dietetic, and exercise regimes were unaltered apart from their water supply.

It is the main purpose of this paper to present a map showing the widely varying sodium concentrations of common drinking-water supplies in Southern Alberta. The features of the terrain that lead to high sodium content in well-water supplies are also described. We hope that these will serve to alert physicians to similar possibilities in their own regions.

Case Reports

Case 1

A 71-year-old man, known to be hypertensive for years, was hospitalized because of progressive shortness of breath on exertion, swelling of the legs and the abdomen, increase in weight and fatigue, and a nonproductive cough for 6 months. The past history was otherwise unremarkable. On examination he showed increased jugular venous pressure, an apex beat in the fifth left interspace in the anterior axillary line, a resting pulse rate of 96 per minute, smooth enlargement of the liver two fingerbreadths below the right costal margin, ascites, marked pitting edema of both legs to above the knees, coarse rales over both lung fields, and a blood pressure of 150/100. No evidence of renal failure was found. The electrocardiogram showed evidence of diffuse myocardial disease and left ventricular predominance.

He improved rapidly on digitalization, mercurial diuretics, and a low-salt diet. Forty pounds in weight were lost over 2 weeks, and he was discharged in compensation. Five months later he moved from Calgary to the country and his general condition worsened considerably, with a rapid increase of 30 pounds in weight. Decompensation was evident as on the previous admission.

After 6 days in the hospital, without any change in regime, he lost 36 pounds in weight and his symptoms were relieved. He insisted that he had followed his low-salt diet faithfully. A sample of well water was tested and contained 4.2 Gm. of sodium per liter (4,200 ppm.) He was discharged home and a new supply of drinking and cooking water of low sodium content was obtained. Since this time he has been completely controlled and no further hospital admissions have been necessary.

Case 2

A 66-year-old clerk, never previously ill, developed angina of effort, but he was able to continue work for almost 2 years, when breathlessness on exertion also appeared. He was admitted from the country in obvious failure, with orthopnea, marked edema of the genitals and legs, and smooth enlargement of the liver to three fingerbreadths below the right costal margin. He was discharged much improved after digitalization and mercurial diuretics by injection.

Two weeks later he was readmitted as ill as before, but these symptoms disappeared after 1 week in the hospital although no change was made in his maintenance therapeutic or dietetic regime.

He reappeared 3 weeks later in severe failure, with paroxysmal nocturnal dyspnea, anasarca, and the liver edge palpable at the right iliac crest.

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Apart from generalized cardiac dilatation and a blowing systolic murmur at the apex no specific abnormalities were found in the heart. The blood pressure was 160/100, and the resting pulse rate ranged around 110 per minute. An electrocardiogram showed atrial fibrillation, a pattern of left ventricular strain, and occasional ventricular extrasystoles. No evidence of renal insufficiency was discovered, and he was considered to have arteriosclerotic heart disease. Again improving rapidly in the hospital, without alteration of his regime he was discharged after 3 weeks only to reappear after 3 weeks in failure once more.

In the hospital he lost 30 pounds in weight and became ambulatory without any change in medications. It was suspected that he could not have followed prescribed treatment, but he was adamant that he had. On testing the water from his private well at home it was found to contain 3.5 Gm. of sodium per liter (equivalent to 5.25 Gm. expressed as common salt). His water supply was changed to one of low sodium content and over the next year he has remained compensated and out of the hospital.

Discussion

Three hundred samples of drinking water, gathered from all parts of Southern Alberta by the Public Health Services for bacteriologic testing, were available for analysis. These are presented in the form of a map (fig. 1) showing their source and range of concentration. They were examined by an adaptation of a serum sodium method on a Beckman Model DU spectrophotometer with a standard flame attachment.

It will be seen that all the river water supplies, which are surface rain water runoff from the Rocky Mountains, have low sodium contents. River water in Alberta in general has a low sodium content in the order of 0 to 50 ppm. (0 to 5 mg. per cent). This includes the supplies for the cities of Edmonton, Calgary, Lethbridge, Medicine Hat, and Drumheller. In winter time this may rise somewhat from the use of soda ash and lime for softening purposes.[1] For example, the sodium chloride content of the water supply of the city of Edmonton remains static at 5 ppm., whereas the sodium sulfate content rises from 8 ppm. in summer to 56 ppm. in winter.

The remainder of the samples were taken almost exclusively from private drilled wells, often from farms; a considerable proportion of these showed very high sodium contents. No seasonal variation in sodium content of well-water supplies could be detected in our series. In general, wells drilled in gravel soil showed a low sodium content similar to that of the rivers. The soils of very well drained surface basins also showed a low sodium concentration. Of the remainder about half showed more than 100 ppm. of sodium, rising as high as 3,500 ppm.

In ancient times the whole of the present plains formed a huge sedimentary basin. Most of this area and much of the central United States were repeatedly covered by seas that joined with the Arctic over what is now the North West Territories, and with the Atlantic in the region of the Gulf of Mexico. At least six successive inundations on this vast scale are known geologically (Cambrian, Ordovician, Silurian, Devonian, Sundance, and Cretaceous Seas).

The soils of Alberta, Saskatchewan, and Manitoba and of the Western United States are often formed by the weathering of these old sedimentary marine rocks and as such contain various alkaline salts.[2, 3] As the mean annual rain fall in Southern Alberta is only 15 inches annually it is sufficient to leach much of the alkaline salts out of the surface top soil, but insufficient to carry them away finally into rivers. As a result the ground water of the prairie Provinces tends to contain high concentrations of alkali. Where natural drainage outlets do not exist, lakes and sloughs form. It is into these that the alkali from the surrounding surface soil is progressively collected.

As drying takes place, surface salt patches occur. Near these the surface soils may have a sodium content as high as 8.0 Gm. per cent and a pH of 10.3. Around such shallow basins the color of the top soil gives a clue to the type of salt content. "White alkali" consists mainly of sodium sulfate, sodium chloride, magnesium sulfate, magnesium chloride, some calcium salts, and small amounts of potassium salts. "Black alkali" is composed mainly of sodium carbonate and bicarbonate, for it dissolves organic materials that produce the

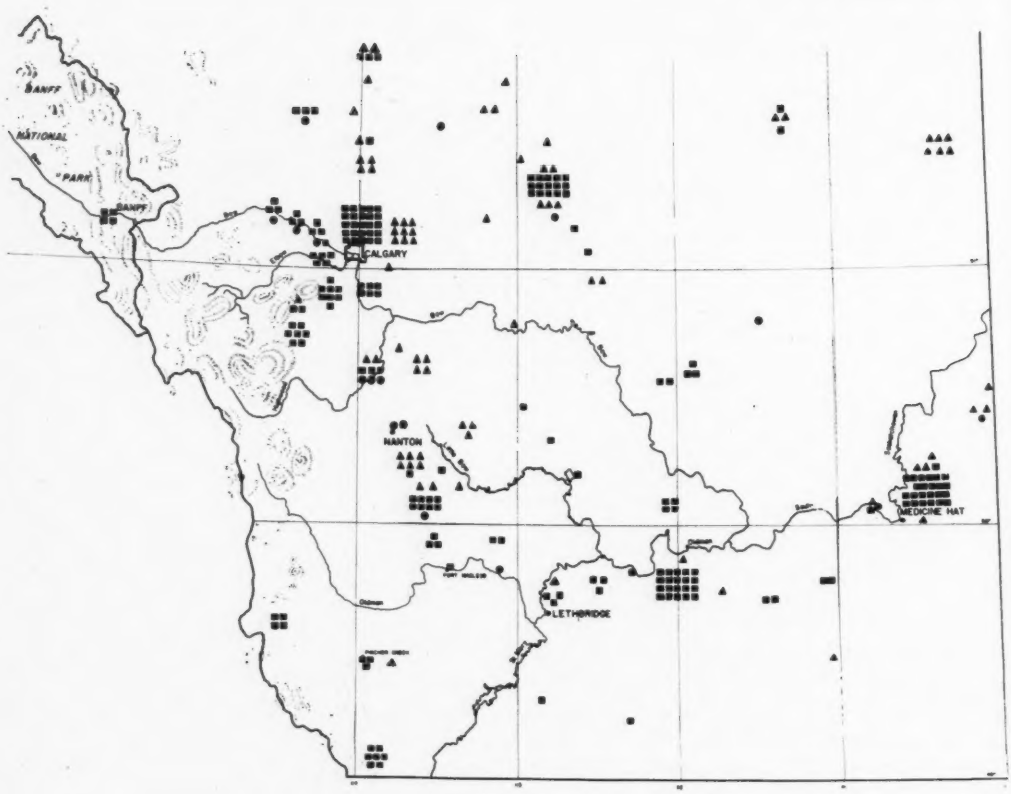

Figure 1

Soduim Concentration of Drinking Water in Southern Alberta. Keys: ■ *0—50 ppm.* ● *50—100 ppm.* ▲ *Over 100 ppm.*

typical color. "Brown alkali" contains a higher proportion of nitrates. Because of its color this is the type that is often unsuspected of salt content. In general, white alkali does not inhibit plant growth unless it exceeds 0.5 Gm. per cent of sodium, "black alkali" will inhibit plant growth in concentrations over 0.1 Gm. per cent. The low salt, dark loams grow vegetations with ease, while black alkaline earths are conspicuously devoid of plant life.[2] These are the key features of alkaline areas and will be easily recognizable to any prairie dweller.

The sodium content of the surface soils is most heavily dependent upon the efficiency of drainage. Even irrigation, with poor outlets, can increase the alkali content of surface soils. It tends to accelerate solution of deeper available salts, and these spread through the more porous superficial layers where evaporation deposits them. Certain marine shales, such as Bear Paw formations, which lie in a rough arc running from east of Edmonton to Lethbridge, have very high sodium contents. Satisfactory water supplies have never been found in marine shales such as these.

It is not always possible, however, to forecast accurately the saline content of overlying soils purely from a knowledge of underlying rock formations. One reason for this is the massive ancient glaciation that extended from the Hudson Bay region almost to the foothills of the Rockies. This tended to carry marine silts over the North West Territories in a

southerly direction and there was a marked mixing of surface soil characteristics over the entire Western Provinces. With the recession of glaciers many old lake basins were formed where early drainage was blocked by glacial morraines. These old lake beds are characterized by the marked fineness of the silt and the extreme flatness of their surfaces. By forming collection basins they acted as enormous salt pans as drying took place. For such reasons water supplies derived from wells of any depth on the prairies may contain surprisingly large amounts of sodium.

Near the mountains, where annual rain fall is around 30 inches, the surface soils are well enough leached to provide low sodium concentrations in all the water we examined. It will be appreciated that with such variable features it has not been uncommon to find closely neighboring private wells showing high and low sodium contents respectively. This has been most useful in arranging better water supplies for cardiac patients.

It is not uncommon in medical literature to see low-sodium diets loosely referred to as low "salt" diets. This tends to focus attention purely upon our most commonly used seasoning. Using 10 hospital personnel chosen at random as tasters, we found that the taste threshold for sodium chloride in water at room temperature was about 500 ppm. of sodium (0.125 Gm. per cent NaCl), for sodium nitrate it was 700 ppm. of sodium (0.25 Gm. per cent $Na\ NO_3$), and for sodium sulfate 1,000 ppm. of sodium (0.25 Gm. per cent Na_2SO_4). Above these levels the latter two solutions tasted "flat" and "brackish" respectively. One taster was a heavy salt eater and his taste threshold for all three salts was about 50 per cent higher than any of his confrères. We also noted that cold solutions were much less easily detected by taste in these concentrations. It is easy to see that sufficient sodium could be present in a patient's diet to reverse the effect of a low-sodium regime, while remaining undetectable by taste in drinking water or in that used for cooking.

In a discussion of low-sodium regimes in the successful management of cardiovascular diseases it has been stated[4] "that those foods which contain more than 100 mg. of sodium per 100 grams of food must be absolutely prohibited." In our study we found that about half the well waters contained over 100 parts per million (10 mg. per cent), ranging widely up to 1,640 ppm. (164 mg. per cent).

This led us to a preliminary survey for sources of low-sodium water supplies for cardiac patients. Much higher sodium concentrations than those quoted above are often found in deep drilling by oil exploration engineers, running as high as 80,000 ppm. (8.0 Gm. per cent). This is equivalent to sea water. The lowest sodium contents were found in run-off rain water or in river water. Where these are not available, snow water may be available in winter time. Ice from water with high sodium content shows practically the same concentration on remelting and is of little use. In actual practice it is worth while surveying the sodium content of several closely adjoining water supplies in a region, for these often vary a great deal. This feature has also been noted in the Province of Manitoba by Ferguson and Kay.[5] There is no doubt that it would be wise to be aware of the sodium content of hospital supplies of drinking and cooking water in all areas, including the effect of their softening systems.

Electrolyte analyses of public water supplies have been reported for medical purposes in Manitoba, but not so far as we are aware in the other Canadian Provinces. The surveys published in the United States concern California,[6, 7] Michigan,[8] Minnesota,[9] Indiana,[10] the Dakotas, Missouri, Texas, Illinois, Ohio, Oklahoma, Arizona[11] and South Carolina.[12, 13]

A good deal has also been published on the sodium content of beverages. A survey made in 1950 by flame photometry of 39 American beers showed low sodium contents, ranging from 10 to 170 ppm., averaging 71 ppm. (7 mg. per cent).[14, 15] In Calgary we found their sodium content to range between 16 to 26 ppm., whereas stout ranged between 170 to 320 ppm.

It is interesting to note that the recorded geographical incidence of cyanosis due to methemoglobinemia in newborn infants is much the same as that of high sodium content in water supplies.[16] This condition is due to excessive intake of nitrate or nitrite, which cannot be fully metabolized at that age. It has been assumed that these salts are obtained from contamination of well-water supplies by seepage from adjacent decaying vegetable matter. However, clearly their source too may be of geological origin.

Summary

A survey of 300 samples of drinking water from Southern Alberta analyzed for sodium content showed that a considerable proportion of well waters contain very high sodium levels, ranging up to 420 mg. per cent (4,200 ppm.).

Two instances of recurrent episodes of heart failure at home, which ceased after substitution of a low- for unsuspected high-sodium water supplies, are described.

The sodium is present in soils derived from underlying marine deposits of seas that covered the whole of the North American plains in ancient times. It is not readily recognizable by taste, especially as sulfate, and may cause darkening of soil so that its presence remains quite unsuspected.

Tasteless sodium in water forms a source of perplexing decompensation in otherwise well-controlled heart disease. The features of the terrain that lead to high sodium content in water supplies are described to alert physicians to similar possibilities in their own regions.

Acknowledgment

This survey would not have been possible without the cooperation of Dr. Dennis Shute, Director, Southern Branch, Provincial Laboratories, Calgary. We wish to acknowledge information on sodium contents of City of Edmonton water supplies supplied by Mr. R. H. Nicholson, Superintendent of their water distribution system.

References

1. Soderman, W. A., and Meyer, D.: The problem of softened water in low salt diets. Missouri Med. 52: 783, 1955.
2. Wyatt, F. A., Bowser, W. E., Odynsky, W., Newton, J. D., and Peters, T. W.: Bulletins 32, 39, 40, 51, University of Alberta, College of Agriculture, 1951.
3. Heber-Cole, L.: The salt deposits of Canada. Dept. Mines & Resources, Ottawa, 1915.
4. Sodi-Pallares, D., Fishleder, B. L., Cisneros, F., Vizcaino, M., Bisteni, A., Medrano, G. A., Polansky, B. J., and de Micheli, A.: A low sodium, high water, high potassium regimen in the successful management of some cardiovascular diseases: Preliminary Clinical Report. Canad. M. A. J. 83: 243, 1960.
5. Ferguson, M. H., and Kay, L. A.: Sodium concentration in drinking water and other fluids, and its significance in restricted sodium intake. Canad. M. A. J. 69: 491, 1953.
6. Cole, S. L.: Sodium in Southern California water. Ann. West Med. & Surg. 5: 177, 1951.
7. Rourke, M. H.: Sodium in special purpose foods and in water: A public health study in California. J. Am. Dietet. A. 36: 216, 1960.
8. McGuire, O. E.: Proceedings of inservice training course in water works problems. University of Michigan School of Public Health, Ann Arbor, Michigan, 1951.
9. Nelson, C. B., Shipman, H. R., and Taylor, D.: Presence of sodium in natural water and softened hard water in relation to low sodium diets. Minnesota Med. 32: 1112, 1949.
10. Bills, C. E., McDonald, F. G., Niedermeyer, W., and Schwartz, M. C.: Sodium and potassium in foods and waters, determination by flame photometry. J. Am. Dietet. A. 25: 304, 1949.
11. Mead Johnson and Company: Sodium and potassium analyses of foods and waters. October 1947. Fifth list.
12. Cole, S. L.: Tap water sodium in the low salt diet. J.A.M.A. 140: 19, 1949.
13. Bailey, K. R.: Sodium content of municipal water supplies of towns and cities of South Carolina. J. South Carolina M. A. 34: 413, 1958.
14. Stone, I., Gray, P. P., and Kenigsberg, M.: Flame photometry—sodium, potassium and calcium in brewing materials. Wallerstein Laboratories Communications 14, 37: 297, 1951.
15. A Wallerstein Laboratories Staff Report "Beer and low-sodium diets." Wallerstein Laboratories Communications 18, 60: 5, 1955.
16. Robertson, H. E., and Riddell, W. A.: Cyanoses of infants produced by high nitrate concentration in rural waters of Saskatchewan. Canad. M. A. J. 60: 230, 1949.

Effect of Exercise on Electrocardiograms of Patients with Low Serum Potassium

By A. J. GEORGOPOULOS, M.D., W. L. PROUDFIT, M.D., AND IRVINE H. PAGE, M.D.

DURING a recent study of the relationship between arterial pressure and exertional angina pectoris in hypertensive patients, it was observed that one patient who had hypokalemia but a normal control electrocardiogram exhibited electrocardiographic signs typical of potassium deficit following exercise.

Because of this incidental observation, further investigation was carried out to evaluate the effect of exercise on the electrocardiogram of patients rendered hypokalemic.

Methods

Twelve adult ambulatory patients with low serum potassium levels were subjected to exercise. Of these, nine had essential and one had malignant hypertension, and two were normotensive. None had a history suggestive of coronary arterial disease. In nine, hypokalemia was secondary to long-term use of chlorothiazide or hydrochlorothiazide for the treatment of hypertension, and in the remaining three, one of whom was normotensive, mild hypokalemia was induced acutely with hydrochlorothiazide for the purpose of this study. Two patients had been on maintenance doses of digitalis.

Exercise was performed in sitting position with use of a stationary bicycle. The duration of each exercise was arbitrarily confined to 1½ minutes. Twelve-lead electrocardiograms (standard limb leads and the precordial leads V_1 through V_6) were taken before and immediately after the exercise. Every 3 minutes thereafter, only the leads best showing the signs of hypokalemia were taken for the next 30 to 45 minutes. The blood pressure was measured sphygmomanometrically in all patients before and after exercise.

All 12 patients were subjected to exercise following potassium depletion; in eight, the electrocardiogram did not suggest hypokalemia, and in the remaining four it was suggestive but not diagnostic of hypokalemia. Serum potassium ranged from 2.8 to 4.2 mEq./L. Of these 12 patients, six were repleted with potassium salts and were subjected to exercise additionally: once when potassium repletion was incomplete (serum potassium ranging from 3.7 to 3.9 mEq./L.) and again when repletion was complete (serum potassium ranging from 4.1 to 4.7 mEq./L.) During repletion, electrocardiograms before exercise were not diagnostic of hypokalemia.

Serum electrolytes were determined by flame photometry in all patients before each exercise and, in four, also 3 minutes following exercise. Normal range is between 4 and 6 mEq./L..

In two patients, during potassium depletion, effects on the electrocardiogram of epinephrine, 5 μg. intravenously, and voluntary hyperventilation for 2 minutes were also studied. The serum potassium in these two patients was 3.2 and 3.5 mEq./L., respectively. The electrocardiograms were suggestive of hypokalemia in both. Twelve-lead electrocardiograms were taken every 3 minutes for a period of 15 minutes.

Results

A. Exercise during Potassium Depletion (Serum K: 2.8 to 4.2 mEq./L.)

In eight patients whose control electrocardiograms during potassium depletion were not diagnostic of hypokalemia, exercise produced electrocardiographic signs typical of hypokalemia in four (fig. 1A and B), suggestive of hypokalemia in two, and in the two patients taking digitalis, exaggerated electrocardiographic signs of digitalis effect. In the remaining four patients whose control electrocardiograms were suggestive of hypokalemia, typical signs of hypokalemia appeared in all immediately following exercise and persisted from 9 to 12 minutes (fig. 2A). The signs of hypokalemia in all patients were best seen in the tracings taken 3 minutes after exercise. The duration of the changes varied from 6 to 15 minutes; the longest was observed in patients with the lowest serum potassium levels (fig. 1A).

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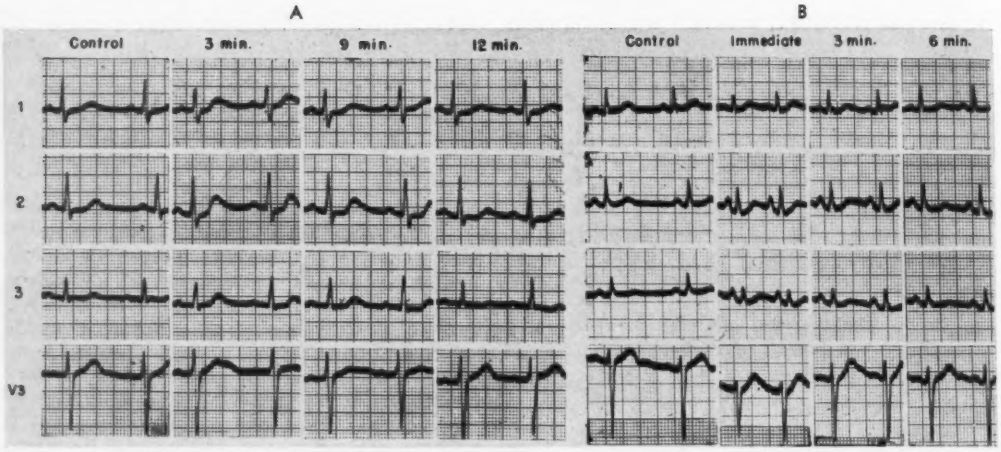

Figure 1

A. Fifty-three-year-old man; average supine arterial pressure 148/98. Serum K: 2.8 mEq./L. B. Thirty-seven-year-old man; average supine arterial pressure 140/96. Serum K: 3.7 mEq./L.

In detail, the electrocardiographic changes produced by exercise were increase in voltage of the P wave from 1 to 2 mm. in two; increase of P-R interval only in the patients taking digitalis; no changes in configuration of the QRS complexes; depression of S-T segment from 0.5 to 2 mm. in nine (mostly in leads II, V_3, V_4, V_5, and V_6) lasting from 3 to 6 minutes; lowering of T in four, especially in the precordial leads; diphasic T waves (in leads II, III, aV_F, V_4, V_5, and V_6) in four; upward deflection of previously inverted T waves in two; fusion of T and U waves in all, except the patients taking digitalis, U-P fusion in three, prolongation of Q-U intervals in all except the patients taking digitalis, atrial premature beats in two, and disappearance of negative U waves present before exercise in one of two patients. In eight, S-T depressions and T-wave changes occurring after exercise fulfill the criteria for an abnormal exercise tolerance test. None of the patients experienced anginal pain during, or after, exercise.

The results obtained were similar in patients rendered hypokalemic acutely or chronically.

In the four patients in whom electrolytes were determined prior to and after exercise, the serum potassium rose by 0.2 mEq./L. in three and 0.4 mEq./L. in one. No significant changes were seen in the serum sodium and chloride. Minor changes occurred in the carbon dioxide content.

In the patients receiving digitalis, the electrocardiographic changes were unusual and quite different from the rest (fig. 2B). The effects of digitalis became more pronounced than on the control tracing. The P wave increased in height considerably and the P-R interval became prolonged. The baseline at the onset of the P wave was deviated markedly upwards as compared with the P-Q segment. The S-T segments were more depressed than on the control tracing. No changes in the QRS complexes were seen. The terminal portion of the T waves was markedly deviated upwards. Possible fusions between P and U waves could not be excluded.

B. Exercise during Incomplete Potassium Repletion (Serum K: 3.7 to 3.9 mEq./L.)

During incomplete potassium depletion, pre-exercise control electrocardiograms were not diagnostic of hypokalemia. Following exercise, one patient showed changes typical

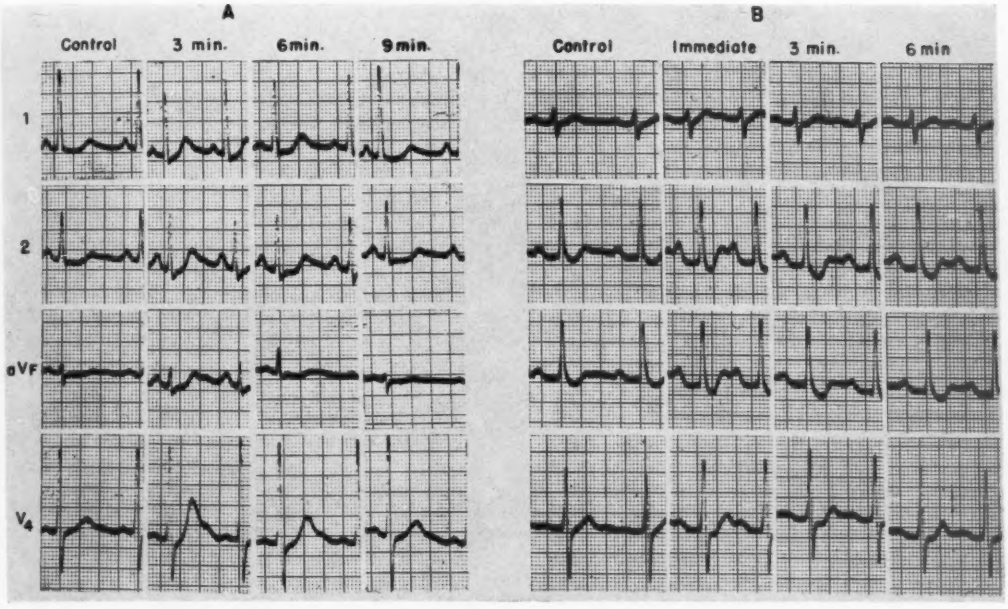

Figure 2

A. *Forty-one-year-old man; average supine arterial pressure 190/120. Serum K: 3.2 mEq./L.* B. *Fifty-three-year-old man; average supine arterial pressure 166/92. Serum K: 3.7 mEq./L. Patient has been taking digitalis regularly for 7 years.*

of hypokalemia and, in the remaining five, the changes were suggestive of hypokalemia; these changes persisted from 3 to 6 minutes (fig. 3B). Again the 3-minute tracings were the most diagnostic. In general, the changes and their duration were less than those observed with exercise during potassium depletion.

As with more pronounced potassium deficit, S-T segment and T-wave changes suggested an abnormal exercise tolerance test in five when the usual criteria for abnormality were applied.

C. Exercise Following Complete Potassium Repletion (Serum K: 4.1 to 4.7 mEq./L.)

Following complete potassium repletion, pre-exercise control electrocardiograms were normal. In five, exercise produced no signs of hypokalemia, no S-T segment depressions, nor T-wave changes. In the remaining patient, minimal changes suggestive of hypokalemia were observed in the tracing taken immediately following exercise but they subsided shortly and did not appear in subsequent tracings (fig. 3C).

D. Additional Studies

Epinephrine (5 μg.) were given intravenously to two patients whose control electrocardiograms were suggestive of hypokalemia. The U waves became slightly taller than before, in almost all leads. In the leads where the T and U waves were fused before, they became separated distinctly from each other for a period of about 6 minutes.

Hyperventilation in two patients, whose control electrocardiograms were suggestive of hypokalemia, produced no changes except for slight sharpening and heightening of T waves in almost all leads.

Blood pressure measurements before and after exercise showed a slight to moderate increase of the systolic and minimal decrease of the diastolic components. These changes are in accord with those reported by others[1] and were independent of the serum potassium level.

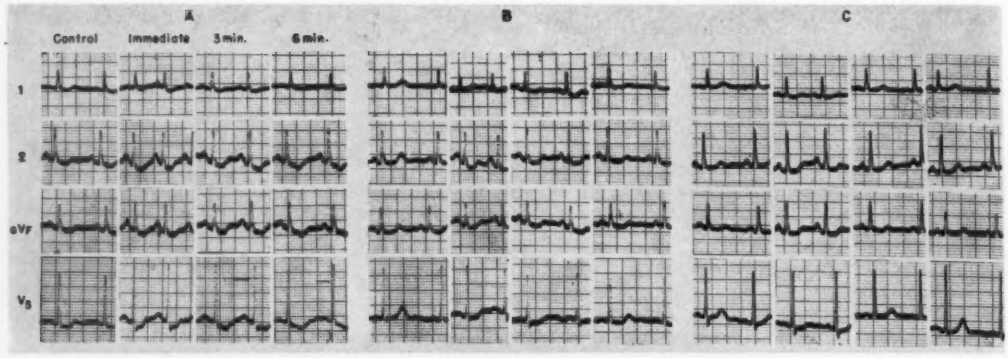

Figure 3

Fifty-two-year-old woman; average supine arterial pressure 130/80. A. *Serum K: 3.5 mEq./L.* B. *Serum K: 3.8 mEq./L.* C. *Serum K: 4.1 mEq./L.*

Discussion

That the electrocardiogram cannot be relied upon as a guide to the diagnosis or treatment of hypokalemia has been previously emphasized.[2, 3] Merrill[4] found that potassium deficit with blood levels of less than 3.0 mEq./L. is recognizable in the electrocardiogram in about 80 per cent of patients. Bellet[5] described various factors that make correlation between the electrocardiogram and serum potassium values difficult.

With the recent widespread use of thiazide compounds in the treatment of hypertension and other conditions, commonly there are patients with chemical evidence of hypokalemia without accompanying electrocardiographic changes. Our study shows that non-strenuous exercise can elicit the electrocardiographic changes of hypokalemia in such patients, even when serum potassium level is at the lower limits of normal.

The electrocardiographic signs observed following exercise in these patients meet all previously reported criteria for the diagnosis of hypokalemia. The severity and duration of the changes closely correlate the degree of hypokalemia, evident especially when comparison is made in the same patient at different levels of serum potassium (fig. 3).

The patients receiving digitalis constituted an exception; following exercise, exaggerated electrocardiographic signs of digitalis effect appeared without signs of hypokalemia. This may be explained by the fact that digitalis produces other changes that obscure the effects of hypokalemia on the electrocardiogram.[5]

The mechanism by which exercise elicits the electrocardiographic changes of potassium deficit is not clear. Exercise in normal rats[6] and rabbits[7] decreases muscular potassium. Denervation of skeletal muscles causes a decreased potassium content,[8] which has been attributed to the resultant fibrillatory contractions. Myocardial contraction, normal or abnormal, is also accompanied by loss of potassium from the fiber.[9, 10] All these studies suggest that exercise is accompanied by a decrease of intracellular potassium in both striated and smooth muscle.

Electrocardiographic signs similar to those seen in hypokalemia have also been produced by intravenous injections of epinephrine,[11] which in cats has been found to produce a decrease of the intracellular potassium concentration of cardiac muscle[12] and a rise in serum potassium.[12, 13] Lepeschkin[14] stated that one of the most constant effects of epinephrine in persons with normal potassium levels is elevation and earlier-than-normal appearance of the U waves. He attributes these to hypokalemia, since they can be prevented by administration of potassium. These effects of epinephrine have been mostly observed in persons with a normal serum potassium level. In our study, however, epi-

nephrine given to two hypokalemic patients did not produce the electrocardiographic signs typical of hypokalemia.

Diphasic T waves and S-T segment depression with prolongation of the Q-T interval may result from hyperventilation with its accompanying alkalosis.[15, 16] Since this might have produced the electrocardiographic changes of hypokalemia following exercise, effects of voluntary hyperventilation without exercise on the bicycle but of equal duration to that of the exercise were studied in two patients. Electrocardiographic signs of hypokalemia were not produced. Hence we conclude that under our conditions, hyperventilation was not an important factor in the production of exercise hypokalemia.

Exercise of hypertensive patients may cause positive U waves and slight prolongation of the Q-T interval,[17, 18] but not the typical signs of hypokalemia. Accordingly, the electrocardiographic changes produced by exercise in these potassium-depleted patients are a function of the potassium deficit and not of exercise alone.

Depressed S-T segments and diphasic T waves occurred frequently following exercise during potassium depletion, but not when repletion was complete. It should be emphasized that these electrocardiographic signs in patients receiving thiazide compounds can be manifestations of hypokalemia and not, necessarily, of ischemic heart disease. Knowledge of the fact that the patient is taking or recently has taken one of these drugs should lead to caution in interpretation of exercise tolerance tests.

Summary

Twelve adult patients (10 hypertensive and two normotensive) with low serum potassium levels but without electrocardiographic signs diagnostic of hypokalemia were subjected to nonstrenuous exercise.

Electrocardiographic signs of hypokalemia appeared following exercise in all but the two hypertensive patients receiving digitalis. The severity of the changes and the duration correlated with the degree of hypokalemia present prior to exercise. The results were similar in the normotensive and hypertensive patients and in those made chronically or acutely hypokalemic. Following potassium repletion, exercise did not produce electrocardiographic changes of hypokalemia.

The frequency with which S-T segment and T-wave changes occurred following exercise during potassium depletion suggested that hypokalemia can introduce an error in interpreting results of exercise tolerance tests in patients receiving thiazide compounds, when serum potassium is at the low normal or borderline level.

These results may reflect intracellular myocardial potassium depletion brought on by exercise.

References

1. Fraser, R. S., and Chapman, C. B.: Studies on the effect of exercise on cardiovascular function. Circulation **93**: 193, 1954.
2. Weaver, W. F., and Burchell, H. B.: Serum potassium and the electrocardiogram in hypokalemia. Circulation **21**: 505, 1960.
3. Schwartz, W. B., Levine, H. D., and Relman, A. S.: The electrocardiogram in potassium depletion. Am. J. Med. **16**: 395, 1954.
4. Merrill, A. J.: The significance of the electrocardiogram in electrolyte disturbances. Am. Heart J. **43**: 634, 1952.
5. Bellet, S.: The electrocardiogram in electrolyte imbalance. Arch. Int. Med. **96**: 618, 1955.
6. Fenn, W. O.: Loss of potassium in voluntary contractions. Am. J. Physiol. **120**: 675, 1937.
7. Fenn, W. O.: Electrolytes in muscle. Physiol. Rev. **16**: 450, 1936.
8. Hines, H. M., and Knowlton, G. C.: Changes in the skeletal muscle of the rat following denervation. Am. J. Physiol. **104**: 379, 1933.
9. Lensi, F., and Caniggia, A.: Nature of myocardial contraction and of action potentials. Acta med. scandinav. **146**: 300, 1953.
10. Calhoun, J. A., Cullen, G. E., Clarke, C., and Harrison, T. R.: Studies in congestive heart failure. J. Clin. Invest. **9**: 393, 1930.
11. Carlton, A.: Experimentally provoked variation of the positive after-potential in the human electrocardiogram. Acta med. scandinav. **146**: 424, 1953.
12. Robertson, W. V. B., and Preyser, P.: Changes in water and electrolytes of cardiac muscle following epinephrine. Am. J. Physiol. **166**: 277, 1951.
13. D'Silva, J. L.: Action of adrenaline-like substances on the serum potassium. J. Physiol. **108**: 218, 1949.

14. LEPESCHKIN, E.: The U wave of the electrocardiogram. Arch. Int. Med. 96: 600, 1955.
15. BARKEN, P. S., SHRADER, E. L., AND RONZONI, E.: The effects of alkalosis and of acidosis upon the human electrocardiogram. Am. Heart J. 17: 169, 1939.
16. THOMPSON, W. P.: The electrocardiogram in the hyperventilation syndrome. Am. Heart J. 25: 372, 1943.
17. YU, P. N. G., BRUCE, R. A., LOVEJOY, F. W., JR., AND PEARSON, R.: Observations on the change of ventricular systole (Q-T interval) during exercise. J. Clin. Invest. 29: 279, 1950.
18. CANNON, P., AND SJÖSTRAND, T.: The occurrence of a positive after-potential in the electrocardiogram in different physiological and pathological conditions. Acta med. scandinav. 146: 191, 1953.

Now that geographical boundaries in our own and in other civilized lands have been determined, the pioneering spirit finds in scientific research enticing vistas for adventure. The twilight zone between what we know and the vast unlimited range of what we do not know presents us with innumerable frontiers. In this zone the opportunities for novel experiences are immensely more abundant than they have ever been in the long history of explorations on land and sea. Here is true pioneering. As in the early days, it imposes on the adventurer who wishes to become an explorer certain demands. What are they?

First among them is resourcefulness. The experimenter tries to imagine conditions that may be encountered; he may not meet them at all, but he may meet others he had not anticipated. New devices may be required to overcome unforeseen difficulties. As the frontiersman may make a corn knife out of a broken scythe blade, or a butcher knife out of a rusty file, or a soap factory from an empty barrel and an iron kettle, so the pioneering investigator may be compelled to use his ingenuity to the limit in adapting available apparatus and materials to the purposes he has in mind.

Another requisite is a forward look and a faith in the efficacy of present and future efforts . . . . In laboratories where experiments are going on, the hopeful "prospect" of the pioneer is still a prime motive. It is related to a characteristic pioneering attitude of the investigator—an unwillingness to be satisfied with what is already known. As Daniel Boone moved onward whenever he could see smoke rising from a chimney, so the worker in science advances toward novel realms of experience. A driving initiative compels him to seek new ventures.

The boundary of knowledge, however, is pushed forward with painful slowness, and always, as an advance is achieved, further territory to be explored is revealed.—WALTER B. CANNON, M.D. *The Way of An Investigator.* New York, W. W. Norton & Company, Inc., 1945, p. 27.

Plasma Heparin Levels

Correlation with Serum Cholesterol and Low-Density Lipoproteins

By H. ENGELBERG, M.D.

SINCE the original observations of the effect of heparin upon the clearing of alimentary lipemia,[1] much data have accumulated that indicate that heparin functions physiologically to facilitate the exit of alimentary triglycerides from the blood. The available evidence on this important question has recently been summarized.[2, 3]

The nature of the heparin lipemia-clearing reaction involves the activation of an enzyme, lipoprotein lipase, which splits the triglycerides of chylomicra and low-density lipoproteins. This activity has been demonstrated in plasma in vitro and in vivo, both after the injection of heparin and endogenously, and, at least in relation to postalimentary lipemia, apparently takes place within the bloodstream or at the capillary wall. The free fatty acids released after triglyceride lipolysis are bound to albumin and rapidly transported to the tissues. The distribution of the other triglyceride component, glycerol, has not been thoroughly investigated. There is much indirect evidence that heparin mobilizes the lipolytic enzyme (apparently present in the capillary wall), stabilizes its activity, and effects its rapid attachment to the chylomicron or lipoprotein substrate.

The heparin lipemia-clearing reaction thus circumvents the hitherto perplexing problem of the barrier that the capillary wall offers to the exit of lipid macromolecules from the bloodstream in all areas except in the liver. This organ may have a direct function in the clearing of alimentary lipemia. There is evidence in rats that the liver removes labeled triglycerides from chylomicra, but this may represent an exchange reaction rather than uptake of chylomicrons. Additional work is necessary to clarify this subject. It is unlikely, however, that the liver has the primary major role in chylomicron removal and dissolution in man, since it does not possess a true lipase and it inactivates lipoprotein lipase. Furthermore, abnormal liver function is not demonstrable in most persons with elevated serum cholesterol and lipoprotein levels.

The reticuloendothelial system is the third pathway which has been proposed for the removal of alimentary lipemia. The available evidence, however, indicates that it functions only in the removal of foreign lipid material, such as fat emulsions, but does not take up normal chyle fat.

Because of the probable physiologic relationship between heparin and fat transport we have been interested in the measurement of circulating endogenous heparin and its correlation with serum lipids. Applying toluidine blue[4] and protamine titration[5] procedures, other workers have also determined heparin-like substances in the blood of atherosclerotic patients but serum lipids were not analyzed, and the methods used are not so much an accurate index of heparin but rather indicators of the equilibrium between the systems of factors favoring or inhibiting coagulation. In our first study we reported an inverse correlation between circulating heparin and low-density lipoproteins.[6, 7] These findings have been corroborated[8] but the data can be questioned, since the heparin values were far above normal,[9] and probably represent heparin plus metachromatic sulfates that were not removed in the analytic procedure. Other papers[10–13] have appeared in which the level of heparinoid substances in the blood of atherosclerotic patients was found to be lower than in normal individuals, but the results are only suggestive, since the methods applied are not specific for heparin.

Subsequent to our original report we pub-

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Table 1

Summary of Average Data

	Heparin levels*	Age groups	Chol. mg.%	Standard low-density lipoproteins in mg. % Sf 0-12	12-20	20-100	100-400	12-400	No. of cases Chol.	Lipo.
	Up to	Up to 50	335	496	64	161	73	298	4	3
M	12	50 & over	273	475	76	161	48	285	9	7
A	12.1 to	Up to 50	263	498	68	162	72	301	35	30
L	15	50 & over	258	508	54	140	66	260	16	15
E	15.1 to	Up to 50	222	473	56	129	52	237	31	27
S	18	50 & over	260	474	57	132	52	240	23	21
	over	Up to 50	241	474	52	110	43	205	18	18
	18	50 & over	229	379	35	78	25	138	11	10
	Up to	Up to 50	240	448	80	169	39	288	4	2
F	12	50 & over	331	690	80	149	80	308	3	2
E	12.1 to	Up to 50	252	492	66	95	18	176	23	11
M	15	50 & over	291	545	77	118	34	223	18	16
A	15.1 to	Up to 50	243	432	37	63	13	113	27	17
L	18	50 & over	292	560	61	86	30	176	25	21
E	over	Up to 50	188	386	28	44	3	79	6	2
S	18	50 & over	259	451	56	47	12	127	7	6

*Heparin levels in units/100 ml., 1 mg. = 100 units.

Table 2

Average Lipid Values at Varying Heparin Levels

	Heparin levels, units %	Cholesterol mg. %	Standard low-density lipoproteins Sf 0-12 mg. %	Sf 12-400 mg. %
	Up to			
M	12	292	481	289
A	12.1 to			
L	15	261	501	287
E	15.1 to			
S	18	238	473	238
	over			
	18	236	440	181
	Up to			
F	12	279	569	298
E	12.1 to			
M	15	269	523	204
A	15.1 to			
L	18	267	502	148
E	over			
S	18	226	435	115

lished an improved technic for the extraction of endogenous plasma heparin.[14] The product obtained contains heparin and chondroitin sulfuric acid. The final assay is based upon anticoagulant activity and therefore only the heparin content of the extract is determined, since chondroitin sulfuric acid has no, or only trace, anticoagulant activity. The use of a biologic assay (with previous dialysis to remove interfering salts) avoids the defects inherent in procedures that involve metachromatic assay. These have been previously discussed,[9] and the reasons have been presented indicating the specificity and superiority of the heparin extraction method used in this study.[14]

Methods

Approximately 50 to 60 ml. of blood were taken from the arm veins of patients after they had been examined in my office, usually in the afternoon, after lunch. Heparin assay was performed in duplicate as previously described[9, 14] on 5-ml. plasma samples, and cholesterol and ultracentrifugal lipoprotein determinations* were made on serum aliquots. The results were discarded if the duplicate heparin determinations deviated more than 15 per cent from the mean,† since this is the variation found in reproducibility studies of this method.[14] Blood was not drawn postabsorptively, since there is no marked change after meals in the three parameters measured. Furthermore, we were interested in the postalimentary relationships between heparin and lipids. It had also been previously established that the in vitro addition of varying concentrations of human low-density serum lipoproteins did not

*These were performed at the Institute of Medical Physics, Belmont, California.

†This occurred in 7.7 per cent of the analyses.

Table 3

Statistical Analysis (r) of Plasma Heparin Levels vs Serum Cholesterol and Standard Sf 0-12 and Sf 12-400 Low-Density Lipoproteins

	Heparin vs cholesterol			Heparin vs Sf 0-12 lipoproteins			Heparin vs Sf 12-400 lipoproteins		
	n	r	p	n	r	p	n	r	p
MALES	147	−0.271	<0.01	131	−0.091	>0.1	131	−0.265	<0.01
FEMALES	113	−0.142	>0.05	77	−0.241	<0.05	77	−0.336	<0.01

Abbreviations: n, number of cases; p, probability; r, Pearson product moment correlation coefficient.

affect the extraction of heparin from aliquots of pooled plasma. Although both normal and atherosclerotic persons were used, certain categories were omitted from this study. These included subjects with liver or kidney disease, thyroid abnormalities, essential hyperlipemia, acute inflammatory or infectious diseases, and patients who were on restricted diets of any type or who were receiving hormone or drug therapy. These groups had variations of factors affecting fat transport other than heparin and the lipemia-clearing enzyme. The use of supplemental vitamins was ignored, as it is widespread, and we have not observed that it has any effect on circulating heparin levels. The age of the patients varied from 26 to 91 years.

Results*

A summary of the average data arranged according to increasing concentrations of circulating heparin, and separated according to sex and age groups, is shown in table 1. There were 147 males and 113 females who had heparin and cholesterol analyses, and 131 males and 77 females of the group also had the lipoprotein determinations. Inspection of the data reveals a decrease in the average lipid values as average heparin levels increase. A simplified set of average values is shown in table 2, and a statistical analysis of heparin versus each of the three lipid parameters in table 3.* All the correlation coefficients are negative. In males the inverse correlation between endogenous plasma heparin on the one hand and serum cholesterol and Sf 12-400 lipoproteins on the other is definitely significant, whereas the correlation of heparin with Sf 0-12 lipoproteins is not significant. In females the relationship between heparin and cholesterol is inverse but is just short of the 5 per cent level of significance. The correlation between heparin and the Sf 0-12 lipoproteins is probably significant, however, and the correlation with the Sf 12-400 lipoproteins is definitely statistically significant.

Discussion

These data were obtained in a fairly large group of people with a more reliable method of heparin extraction than that used in our

*The individual data of heparin levels, cholesterol, and lipoproteins have been deposited as Document number 6523 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35-mm. microfilm. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

*I am indebted to Dr. Morton I. Grossman for help with the statistical calculations.

earlier study.[7] They demonstrate a statistically significant inverse correlation between endogenous plasma heparin and serum low-density Sf 12-400 lipoproteins and cholesterol. This is physiologically important in view of the involvement of heparin in the enzyme system that probably has an important role in the removal of alimentary neutral fat from the bloodstream in man. Although the serum transport phase of fat metabolism is undoubtedly complex, with many dynamically interacting events, the results afford substantial evidence that a relative insufficiency of circulating heparin is one of the important etiologic factors leading to hyperlipoproteinemia, hypercholesteremia, and atherosclerosis.

The negative correlation coefficients between circulating heparin and lipids, though definitely significant, are, however, relatively low numerically. Therefore, there are other factors exerting powerful influences upon serum lipids. We may speculate upon these, since they are the basis for further investigation. Lipoprotein lipase, in addition to heparin, contains a tissue factor that is probably the true lipolytic moiety. The availability of this apoenzyme to the mobilizing action of heparin undoubtedly affects the resultant enzymatic activity, and apoenzyme deficiency has been reported.[15] It could also be that adequate supplies of heparin and tissue factor exist but that other substances competitively bind heparin, so that lipoprotein lipase formation is inhibited. Lipoprotein lipase itself may be present in adequate quantity but inhibitors might interfere with its lipolytic activity. It is also well to remember that there is no evidence of impaired triglyceride clearance in subjects with cholesterol elevations of the essential hypercholesteremia type. Thus there is no reason to believe that heparin deficiency would be present in these individuals who constitute a substantial fraction of patients with increased serum cholesterol levels.

Other workers[8] have reported a significant negative correlation between plasma heparin and Sf 0-12 and Sf 12-20 lipoproteins, but not between heparin and lipoproteins above Sf 20, nor with the high-density lipoproteins. Our findings, however, showed a statistically significant negative correlation between circulating heparin and Sf 12-400 lipoproteins in both sexes, whereas a probably significant relationship with Sf 0-12 lipoproteins was found only in females. In addition to their application of a method that is not specific for heparin, as discussed earlier in this paper, the discrepancy may lie in their use of fasting subjects who show a trend toward higher Sf 0-12 and lower Sf 20-400 lipoprotein levels.[16] The more significant negative correlation of endogenous heparin with the Sf 12-400 lipoproteins, rich in triglyceride, which our data show, is consonant with all pharmacologic studies with injected heparin, which demonstrate that lipoproteins of Sf 20 and higher are those primarily affected by the heparin-activated lipase. Studies of endogenous plasma lipemia-clearing factor in nonfasting subjects have also shown a significant inverse relationship to the Sf 12-004 lipoproteins but not to the Sf 0-12 class.[17]

It may be argued that the lipoproteins affect the level of circulating heparin rather than vice versa, but there is some evidence against this possibility. It has been found that intravenous fat infusions in man result in an increase in plasma heparin levels in the majority of subjects.[18] Oral fat feedings do not decrease circulating heparin.[19] Futhermore, individuals with nephrosis, hypothyroidism, or essential hyperlipemia, who have markedly elevated serum lipids, do not have low values of plasma heparin.[20] Finally, the reduction of serum lipids by strict low-fat diets does not affect heparin levels.[20] It is therefore more reasonable to consider that the heparin content of the plasma is the primary factor in the inverse relationship between heparin and serum lipids.

Summary

Endogenous plasma heparin was determined in 147 males and 113 females. Serum cholesterol was measured in the entire group, and low-density lipoproteins were ultracentrifugally analyzed in 131 males aud 77 females.

Statistical analysis of the data showed a definitely significant ($p<.01$) negative correlation between heparin on the one hand and serum cholesterol and Sf 12-400 lipoproteins on the other in males.

In females the correlation between heparin and cholesterol was negative but fell short of the 5 per cent level of significance. The correlation between heparin and Sf 12-400 lipoproteins was negative and statistically definitely significant ($p<.01$). The correlation with the Sf 0-12 lipoproteins was also negative and probably significant ($p<.05$).

These results afford substantial evidence that a relative deficiency of circulating heparin is one of the important causative factors leading to elevated levels of serum lipid.

References

1. Hahn, P. F.: Abolishment of ailmentary lipemia following injection of heparin. Science **98**: 19, 1943.
2. Robinson, D. S.: The heparin clearing reaction. Am. J. Clin. Nutrition **8**: 7, 1960.
3. Engelberg, H.: Heparin lipemia clearing reaction and fat transport in man. Summary of available knowledge. Am. J. Clin. Nutrition **8**: 21, 1960.
4. Salvini, L., and Scardigli, G.: Variations of heparin activity in various diseases. Gior. clin. med. **31**: 1505, 1950.
5. Nikkila, E. A., and Majanen, S.: Protamine titration in atherosclerotic individuals. Scandinav. J. Clin. & Lab. Invest. **4**: 204, 1952.
6. Engelberg, H.: Further studies of human circulating plasma heparin levels. Correlation with serum lipids and lipoproteins. Circulation **8**: 448, 1953.
7. Engelberg, H.: Correlation of plasma heparin levels with serum lipoproteins. Acta med. scandinav. **151**: 161, 1955.
8. Yasugi, T., Gofman, J. W., de Lalla, O., Tamplin, A. R., and Oshima, K.: Relationship of blood heparin levels to serum lipoproteins and cholesterol. Proc. Soc. Exper. Biol. & Med. **98**: 46, 1958.
9. Engelberg, H.: Plasma heparin levels in normal man. Circulation **23**: 578, 1961.
10. Pescador, L., Outeirino, J., de Prados, M., and Sainz, V.: Physopathology of heparin; its relation to cholesterol in conditions of vascular atheromatosis. Rev. clin. espan. **56**: 15, 1955.
11. Antonini, F. M., and Salvini, L.: Mucopolysaccharides, clearing factor, age and arteriosclerosis. Bull. schweiz. Akad. med. Wissensch. **13**: 209, 1957.
12. Coppo, D. M., Vecchi, G. P., and Lorenzini, R.: Dati attuali sulla parte svolta dai lipidi nell arteriosclerosi. Bull. schweiz. Akad. Med. Wissensch. **13**: 179, 1957.
13. Thomas, W. A., and Olwin, J. H.: Variations in protamine titration results in the blood of atherosclerotic patients. Angiology **9**: 279, 1958.
14. Engelberg, H., Dudley, A., and Freeman, L.: An improved method for the determination of plasma heparin. J. Lab. & Clin. Med. **46**: 653, 1955.
15. Havel, R. J.: Transport and metabolism of chylomicra. Am. J. Clin. Nutrition **6**: 662, 1958.
16. Tamplin, A. R., and Tandy, R. K.: Serum lipoprotein statistics in populations and individuals. J. Appl. Physiol **15**: 145, 1960.
17. Engelberg, H.: Human endogenous plasma lipemia clearing activity. Observations in 482 individuals. J. Appl. Physiol. **13**: 375, 1958.
18. Engelberg, H.: Plasma heparin levels in man following intravenous fat emulsions. Proc. Soc. Exper. Biol. & Med. **97**: 304, 1958.
19. Engelberg, H.: Human plasma heparin levels and lipemia clearing activity after ingestion of animal and vegetable fat. J. Appl. Physiol. **13**: 296, 1958.
20. Engelberg, H.: Unpublished observations.

Plasma Heparin Levels in Normal Man

By H. ENGELBERG, M.D.

With the technical assistance of Anne Dudley

THE DETERMINATION of the level of circulating endogenous heparin is important, since heparin may normally function to keep the blood in a fluid state, and it also probably plays a major role in the clearing of alimentary lipemia from the bloodstream. Unfortunately, methods for the extraction of native heparin are not only difficult and tedious, but the end-product includes other mucopolysaccharides that interfere with assays based upon metachromatic technics.[1] On the other hand, coagulation tests, such as the protamine titration and toluidine blue procedures, are not an index of the amount of heparin but rather indicators of the equilibrium between the systems of factors favoring or inhibiting blood clotting.[2] A relatively simple procedure[3] based upon thrombin neutralization is available, but it is only discriminating enough to disclose marked increases in heparin levels. There are excellent methods[4] for measuring the levels of injected, free heparin, but these do not afford information about the quantity of endogenous plasma heparin, which, with rare exceptions, is always protein-bound.

These various difficulties, and the failure to appreciate them, have led to marked discrepancies in the results reported in studies of circulating heparin. Some responsible investigators[4] imply that heparin is not normally present in human plasma, whereas others[5] have reported very high levels. It seems to have been overlooked that years ago large quantities of plasma were extracted with use of established methods for the isolation of heparin from tissues[6] and anticoagulant substances were found in human plasma in quantities ranging from 0.53 to 1.5 mg. per liter.[7, 8]

We have been interested in this problem since 1952, and have published several methods for the isolation of native plasma heparin from small quantities of plasma.[9, 10] The following facts afford good evidence that the substance isolated from plasma is heparin: 1. It is precipitated by octylamine. 2. It is stable despite boiling; this is characteristic of heparin. 3. It has anticoagulant, antithrombic, and metachromatic activity despite prolonged dialysis, which removes all salts that could possess anticoagulant or metachromatic properties. 4. Protamine sulfate neutralizes the anticoagulant activity. 5. Electrophoretic studies on toluidine blue paper established the presence of heparin in the extract. 6. The extraction method affords a 76 per cent recovery of injected heparin and an 82.5 per cent recovery of heparin added to plasma in vitro. The final extract probably contains other sulfated mucopolysaccharides such as chondroitin sulfate but, since the latter has only trace anticoagulant activity if any, it does not contribute to the final assay, which is based on anticoagulant technics. This type of biologic assay also avoids the lack of specificity of all metachromatic procedures. These results proved that anticoagulant heparin is a normal constituent of human blood, a finding independently and almost simultaneously confirmed by others.[12]

Although our method is laborious, and duplicate assays may vary up to 15 per cent from the mean, we have persisted in its use because of the inherent defects of other published methods that use practical amounts of plasma. We were unable to obtain reliable duplicate determinations with the method of the Scandinavian workers.[12] Another frequently applied technic[13] involves metachro-

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matic assay and also does not adequately eliminate salts that may have metachromatic effects themselves. A more recent method[5] is not applicable to routine heparin determinations, since it involves the injection of radioactively labeled sulfate. Furthermore, inadequate proof was given by the authors that the labeled material they isolated from the blood was endogenous heparin, since commercial heparin had been added as a carrier in the extraction procedure.

Method

Briefly the method[10] we have applied is based upon tryptic digestion of the total plasma proteins previously precipitated by methanol-acetone, overnight dialysis after heat denaturation of the enzyme, and subsequent lyophilization or evaporation. The anticoagulant assay[9] was performed with recalcified sheep plasma according to the U.S.P. XIV technic for heparin. Slight improvements in the procedure have been previously described.[14] All analyses were performed in duplicate on aliquots of citrated or oxalated plasma, and the results were discarded if there was over 15 per cent deviation from the mean. In the past 4 years in our hands this occurred in 53 samples from a total of 680 subjects, giving a 7.7 per cent incidence of invalid results due to inadequacies in the method. Blood was not drawn in the postabsorptive state in this study, as we have not observed any significant change in heparin levels after meals.[15] Washings of the blood cells were not made, as they are when free or added heparin is determined,[4] since we have not found heparin to be present when red cells are hemolyzed.

Table 1

Heparin Levels in Serum and Plasma Aliquots

Subject		Heparin in units %	
Sex	Age	Serum	Plasma
M	32	15.0	14.0
M	46	14.5	15.3
M	43	15.0	15.6
M	62	15.5	15.5
F	51	12.8	17.5
M	45	18.0	18.3

Results

The heparin levels of serum and plasma aliquots in six persons are shown in table 1.

Except for one subject there was no significant difference between serum and plasma. It has seemed desirable to use plasma, since heparin may be involved in the coagulation process. Table 2 presents the average plasma heparin levels and the range of values in 153 males and 103 females, grouped according to age decades. The values are in units per cent based upon the international standard for heparin, 1 mg. = 100 units. There was no sex difference and no apparent age trend except for a slightly higher level in the oldest men. The number of subjects over 80 is too small, however, for this slight difference to be significant.

Discussion

The plasma extract obtained by this technic may not be a single chemical substance. It

Table 2

Plasma Heparin Levels in Units Per 100 ml. in Clinically Normal Individuals

	Age in Decades	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
MALES	No. of Subjects	16	16	24	49	30	10	5	3
	Average Heparin Level	15.8	16.5	15.3	16.0	15.7	15.8	16.3	17.7
	Range of Heparin Values	12.0 to 21.0	11.5 to 24.0	10.5 to 20.5	10.0 to 22.2	11.4 to 19.8	13.1 to 18.0	11.9 to 19.5	15.5 to 20.7
FEMALES	No. of Subjects	10	13	21	24	16	9	5	3
	Average Heparin Level	16.4	16.2	15.4	15.3	16.6	15.5	16.8	16.3
	Range of Heparin Values	13.8 to 23.2	11.8 to 20.6	10.6 to 19.8	12.3 to 17.8	11.8 to 19.7	12.5 to 17.8	14.2 to 19.3	12.8 to 19.7

is well known that the degree of sulfation and the anticoagulant activity of various heparins differ. The probable lack of homogeneity of the heparins in the extract is unimportant, however, in view of the final assay, which is based upon anticoagulant activity. We are interested in assessing the possible physiologic activity of plasma heparin, and a biologic assay affords the best approach in that direction.

The range of values we have found is in accord with the results of earlier investigators,[7, 8] who extracted large volumes of human plasma with standard technic for the extraction of heparin from tissues. They reported 0.53 to 1.5 mg. of heparin per liter of plasma. It can be seen from table 2 that the range of plasma heparin obtained with our method is 1 to 2.4 mg. per liter, with average values of 1.53 to 1.77 mg. per liter. It is also interesting that an estimate based upon the relationship between clotting time and heparin concentration, and the effect of protamine on the normal clotting time, arrived at a probable heparin content of normal blood of the order of 0.1 unit per ml. (1 mg. per liter).[16] Our results are also compatible with the levels reported with an entirely different method of heparin extraction[12] and with those obtained by determinations of total acid mucopolysaccharides in normal serum in which an average level of 2.7 mg. per liter (measured as glucuronic acid) was found.[17] The acid mucopolysaccharides contained two main components, identified by paper chromatography as chondroitin sulfuric acid and heparin plus B-heparin. It would appear therefore that the evidence obtained by various approaches places normal plasma heparin levels in the range we have presented. Similar values have been found in rats.[18] The development of better methods may delineate the range of normal values more precisely, but there is no substantial justification for doubts about the normal presence of heparin in the blood.

It is unfortunate that we have no measurements in children below 10 years of age. There is some evidence, obtained with a toluidine blue method that is not specific for heparin, that plasma heparin is somewhat higher in the newborn but is at levels similar to adults after the age of 3 months.[10] Our results do not show any variation with age in any decade except for the possible higher level found in men above 80 years, nor is there any difference between the sexes.

Summary

Endogenous plasma heparin levels were determined in duplicate in 153 males and 103 females.

Heparin is normally present in human plasma in values ranging from 10 to 24 units per cent (1 to 2.4 mg. per liter). The range of average values was from 1.53 to 1.77 mg. per liter.

No age or sex difference was found.

References

1. Gibson, R. B., Carr, T. L., Green, S., and Fowler, W. M.: Photometric assay of plasma heparin. Proc. Soc. Exper. Biol. & Med. 79: 577, 1952.
2. Avogaro, P., and Caturelli, G.: Meaning and limits of the heparin activity test of plasma. Acta med. patavina 15: 135, 1955, in Chem. Abstracts, Sept. 25, 1956, no. 13158.
3. Quick, A. J.: Hemorrhagic Diseases. Philadelphia, Lea & Febiger, 1957, pp. 328 and 431.
4. Monkhouse, F. C., and Jaques, L. B.: An improved method for the extraction of heparin from blood. J. Lab. & Clin. Med. 36: 782, 1950.
5. Eiber, H. B., and Danishefsky, I.: Heparin in blood. Proc. Soc. Exper. Biol. & Med. 94: 801, 1957.
6. Charles, A. F., and Scott, D. A.: Studies in heparin. I. The preparation of heparin. J. Biol. Chem. 102: 425, 1933.
7. Wilander, O.: Studien uber Heparin. Skandinav. Arch. f. Physiol. **Suppl. 15**, 1938.
8. Astrup, P.: On the determination of heparin in blood plasma and urine. Acta pharmacol. et toxicologica. 3: 165, 1947.
9. Freeman, L., Engelberg, H., and Dudley, A.: Plasma heparin levels. 1. A method for determination of plasma heparin based on anticoagulant activity. Am. J. Clin. Path. 24: 599, 1954.
10. Engelberg, H., Dudley, A., and Freeman, L.: An improved method for the determination of plasma heparin. J. Lab. & Clin. Med. 46: 653, 1955.
11. Schiller, S.: The isolation of chondroitinsul-

phuric acid from normal plasma. Biochimica et biophys. acta. **28**: 413, 1958.

12. NILSSON, I. M., AND WENCKERT, A.: Demonstration of a heparin-like anticoagulant in normal blood. 1. Human blood. Acta med. scandinav. **150**: Suppl. 297, 1955.
13. BASSIOUNI, M.: The estimation of heparin in blood. J. Clin. Path. **6**: 39, 1953.
14. ENGELBERG, H.: Plasma heparin levels in man following intravenous fat emulsions. Proc. Soc. Exper. Biol. & Med. **97**: 304, 1958.
15. ENGELBERG, H.: Human plasma heparin levels and lipemia clearing activity after ingestion of animal and vegetable fat. J. Appl. Physiol. **13**: 296, 1958.
16. BEST, C. H.: Heparin and thrombosis. Harvey Lectures, **36**: 66, 1940-41.
17. BOLLET, A. J., SERAYDARIAN, M. W., AND SIMPSON, W. F.: Acid mucopolysaccharide in normal serum. J. Clin. Invest. **36**: 1328, 1957.
18. MARX, L., HIROTA, M., PRINTUP, C. A., WARNICK, M. A., AND MARX, W.: Effects of exposure to 5°C and advancing age on tissue mast cells and heparin in male rats. Am. J. Physiol. **198**: 180, 1960.
19. ANGELII, B., AND GRASSO, E.: Determination of heparin in the plasma of the new-born and of normal children with toluidine blue. Minerva pediat. **3**: 147, 1951, in Chem. Abstracts, no. 7613, 1952.

Water

And it is especially worthy of note that of earth, air, fire, and water the last is the only one which happens to be an individual chemical compound. From that day to this the unique position of water has never been shaken. It remains the most familiar and the most important of all things.

Within a comparatively recent time, to be sure, it has definitely lost its claim to be a true element, in the modern sense, but meanwhile almost every great development of science has contributed to make its importance more clear. In physics, in chemistry, in geology, in meteorology, and in biology nothing else threatens its preëminence. The physicist has perforce chosen it to define his standards of density, of heat capacity, etc., and as a means to obtain fixed points in thermometry. The chemist has often been almost exclusively concerned with reactions which take place in aqueous solution, and the unique chemical properties of water are of fundamental significance in most of the departments of his science. In geology neptunism has at length won a certain though incomplete triumph over plutonism, and the action of water now appears to be far the most momentous factor in geological evolution. The meteorologist perceives that the incomparable mobility of water, which depends upon its peculiar physical properties and upon its existence in vast quantities in all three states of solid, liquid, and gas, is the chief factor among the properties of matter to determine the nature of the phenomena which he studies; and the physiologist has found that water is invariably the principal constituent of active living organisms. Water is ingested in greater amounts than all other substances combined, and it is no less the chief excretion.—LAWRENCE J. HENDERSON. *The Fitness of the Environment.* New York, The MacMillan Co., 1924, p. 72.

The Mechanical Consequences of Anomalous Atrioventricular Excitation (WPW Syndrome)

By HAROLD W. MARCH, M.D., ARTHUR SELZER, M.D., AND HERBERT N. HULTGREN, M.D.

SINCE its description as a clinical entity in 1930,[1] the Wolff-Parkinson-White (WPW) syndrome has been the object of much study and speculation. The essential feature of the disorder is early anomalous activation of at least a portion of the ventricular myocardium as indicated by the "delta" deformity of the QRS complex. Shortening of the P-R segment to 0.12 second or less is accompanied by varying degrees of prolongation or aberration of the QRS complex. Exidence has been adduced in support of the hypothesis that preactivation occurs via a functioning accessory atrioventricular conduction pathway.[2-6]

The mechanical consequences of this unique abnormality have received less attention. A number of technics have been employed in previous studies. Prinzmetal and co-workers[7] used a high-speed movie camera during electrical stimulation of dog ventricles, and observed a localized area of contraction preceding the normal contraction wave in the same ventricle. Pick and Katz[8] have questioned, however, whether true WPW complexes were produced. Bandiera and Antognetti,[9] employing an improved method or roentgenkymography, reported precontracting areas high in the ventricle, on the left side when the electrocardiogram exhibited predominantly positive QRS complexes in right precordial leads (type A),[10] and on the right side when predominant S waves were recorded in the same leads (type B).[10] Curiously, the same aberrant border motion persisted when the WPW morphology was replaced by normal complexes.

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A different point of view has been presented by Ferrer and co-workers.[11] The intervals from the Q wave of the electrocardiogram to the onset of pressure rise in the right ventricle ($Q\text{-}RV_s$), and from Q to brachial artery pressure rise ($Q\text{-}BA_s$) were measured in two patients with WPW undergoing cardiac catheterization. The authors concluded that in each case systole was delayed in both ventricles, and that neither ventricle was normally activated. But in the presence of the characteristic initial deformity of the QRS complex whose origin, time course, and relationship to the main process of activation are not established, it would appear more logical to relate mechanical activity to a portion of the electrocardiogram that is normal, namely the P wave. Measured in this way, i.e., $P\text{-}RV_s$, activation of the right ventricle in the first case would be on time, whereas the distinct possibility remains that it would be delayed in the second case. Similarly, the argument for delayed BA_s would be stronger if it could be shown that the delay occurred with relation to the onset of atrial activity.

Samet el al.[12] studied both types of WPW syndrome by electrokymographic records of aorta and pulmonary artery motion. Movement of the aortic shadow preceded that of the pulmonary artery in three of seven type-A cases, and the reverse was true in two of six type-B cases, but regardless of the presence of asynchrony, ejection was delayed on both sides of the heart in all cases studied. Dack et al.,[13] using a similar technic, could not establish significant asynchrony in any of four patients. But in electrokymograms there may be difficulty in distinguishing between intrinsic border motion as distinct from movements of the heart generally, especially in

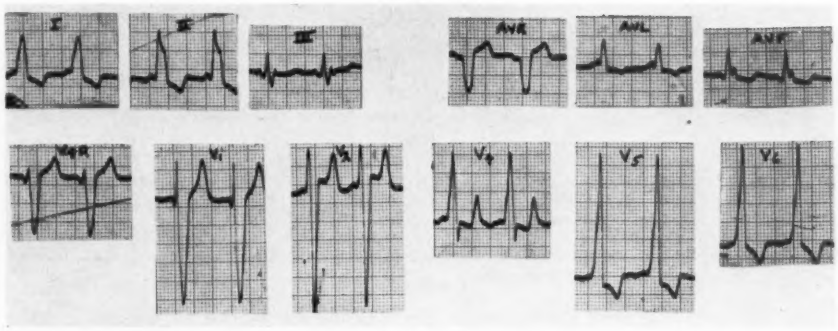

Figure 1

Case 1. Twelve-lead electrocardiogram showing WPW conduction, type B. The fine time lines indicate 0.04-second and the heavy lines 0.20-second intervals in this and subsequent figures.

curves taken from the ascending aorta or arch.[12]

Wolferth and Wood[2] recorded the jugular phlebogram in a patient during WPW conduction and observed a bifid "c" wave in which the peaks were separated by a 0.09-second interval.[2] The second summit was simultaneous with the carotid upstroke and the first peak was ascribed to early pressure rise in the right ventricle. Unfortunately no control data were available. Moia and Inchauspe[14] and Cossio et al.[15] have also studied the jugular pulse, submitting as evidence of asynchrony either that the "a"-"c" interval was shortened or that the "v" wave crest was early with WPW beats. The illustrations were not clear, and again no control information was offered. Scherf and Schonbrunner[16] reported a longer Q-carotid upstroke interval with WPW beats compared with the patient's normal beats. But the onset of P to onset of carotid pressure rise appeared to remain constant, suggesting that ejection time is unchanged with respect to the start of atrial activation.

Kossmann and Goldberg[17] published the phonocardiogram and carotid pulse of a case in which WPW and normal beats alternated, concluding from their material that both ventricles were anomalously excited, because the "intrinsicoid" deflection was delayed in all precordial leads. The second sound was up-

split with WPW beats, but with normal beats, pulmonic closure was distinct from and later than aortic closure. Although P-CA_s was shorter with WPW beats, Q-CA_s was longer with anomalous conduction as was the Q-T interval of the electrocardiogram. It was concluded that ejection from the left ventricle was delayed in a manner that simulated left bundle-branch block. But this view appears inconsistent with the type of second sound splitting described, which suggests only that with WPW beats, pulmonic valve closure comes earlier. Öhnell[18] included two phonocardiograms in his long monograph, showing impurity of the second sound with WPW beats but carotid pulses were not inscribed and the sequence of valve closure could not be determined.

Material and Methods

Since it has been questioned whether experimentally induced fusion beats of the WPW type really pertain to the mechanism of the human disorder, it would seem that further study by the clinical technics of phonocardiograms, pulse recordings, and cardiac catheterization would be useful, especially when the subject can act as his own control by furnishing both normal and anomalous complexes.

When the atrioventricular values are normal and heart failure is not present, the first sound is practically simultaneous with the onset of ventricular systole. This event usually occurs earlier on the left side, and distinct mitral and tricuspid components of the first sound may be identified,

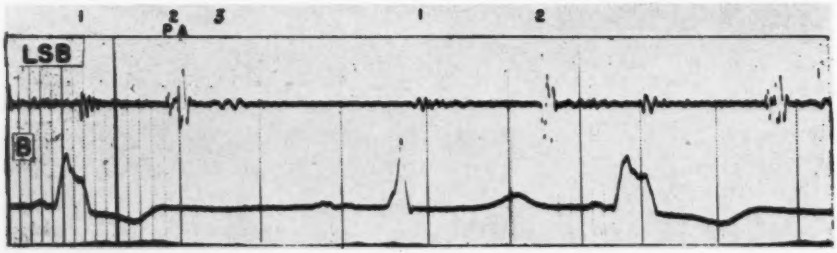

Figure 2

Case 1. Note split of second sound with WPW beats in contrast to "normal" beats.

but the separation does not exceed 0.02 to 0.03 second.[19] A wider separation of these components strongly suggests abnormal ventricular asynchrony. In this regard it is important not to mistake an atrial gallop or an ejection sound for a component of a truly split first sound. When the second sound is not a single deflection, the end of systole on each side may be timed from the incisura of the carotid pulse, which identifies the component due to aortic valve closure. In phonocardiograms recorded during expiration, pulmonic closure follows aortic by 0.03 second or less, and a prolongation of this interval suggests delayed ejection on the right, early completion of ejection on the left, or both. These considerations are true in reverse when the splitting is paradoxical and pulmonic closure precedes aortic. For reasons already discussed, it is here considered preferable to use the normal onset of the P wave as a reference point for the following intervals: P-1st sound (P-S1), or ($P\text{-}S1_m$ and $P\text{-}S1_t$) when mitral and tricuspid components can be identified, P-2nd sound (P-S2), or ($P\text{-}S2_a$ and $P\text{-}S2_p$) when aortic and pulmonic components are identifiable, P-carotid artery upstroke ($P\text{-}CA_s$), and P-carotid artery incisura ($P\text{-}CA_i$). A delay of 0.01 to 0.03 second between the aortic closure sound and the carotid incisura is usually present and represents the transmission time along the carotid artery and through the recording apparatus. The latter element is negligible.

Twelve patients with WPW syndrome have been studied in this manner. The 12-lead electrocardiograms were recorded with the Sanborn direct writer. Phonocardiograms and carotid sphygmograms were recorded mainly with the Sanborn "Twin-Beam" but a few of the older studies were done on the Sanborn Tribeam. The sphygmograph transducer was of the crystal type. Apex cardiograms and jugular pulses were usually available but were generally noncontributory. Collateral information from cardiac catheterization was available in one of these patients.

Results

Three patients had phonocardiograms recorded both during WPW and during normal conduction, and in one of them alternation of both types of conduction was present while cardiac catheterization was being performed. Their data are presented first.

Case 1

E. G., was an 8-year-old girl with congenital disease of the mitral valve. A probable history of paroxysmal tachycardia was elicited. The 12-lead electrocardiogram in figure 1 exhibited WPW conduction. The P-R interval was 0.08 second, the QRS complex was aberrant, and its duration was 0.14 second. Prominent delta waves were evident in the left precordial leads, and in V_1 a small qR deflection was followed by a deep S wave. The configuration was suggestive of type-B WPW, in which early excitation was thought to occur on the right side.

While the phonocardiogram was being recorded, it was noted that the type of conduction was alternating. The first and third complexes of figure 2 were similar to lead II in figure 1, representing WPW conduction. In the alternate complex, however, the P-R interval was prolonged to 0.18 second and the QRS complex was 0.06 second. Conduction was more normal in these complexes but there was actually persistence of the delta wave. On another occasion a completely normal qR wave was recorded in lead II.

Nevertheless, distinct changes occurred in the phonocardiogram. In figure 2 recorded at the left sternal border, the second sound was essentially pure during "normal" conduction, but distinct splitting was present with the WPW complexes. It should also be noted that the first sound deflections were small and poorly defined with "normal" conduction, whereas they were of considerable amplitude with WPW beats. Moreover, these deflections began 0.05 second earlier in the WPW

Table 1

Data for Case 1. (E. S., 9-year-old girl)

	WPW	Normal
Electrocardiogram		
P-R, second	0.08	0.18
QRS	0.14	0.08
P-S	0.22	0.24
Phonocardiogram		
P-S1, second	0.19	0.24
$P\text{-}S2_p$	0.50	
$P\text{-}S2_a$	0.54	0.56
Mechanical events		
$P\text{-}CA_a$, second	0.30	0.32
$P\text{-}CA_i$	0.56	0.60
P-RV	0.16	0.20
$P\text{-}FA_a$	0.35	0.36
$P\text{-}FA_i$	0.58	0.61

Abbreviations: P-R, interval from onset of P to onset of R. P-S, onset of P to end of S wave. P-S1, onset of P to main deflection of first sound. $P\text{-}S2_p$, onset of P to pulmonic closure sound. $P\text{-}S2_a$, onset of P to aortic closure sound. $P\text{-}CA_a$, onset of P to carotid pulse upstroke. $P\text{-}CA_i$, onset of P to carotid pulse incisura. P-RV, onset of P to right ventricular pressure rise. $P\text{-}FA_a$, onset of P to intrafemoral pressure rise. $P\text{-}FA_i$, onset of P to intrafemoral incisura.

cycles. Pulmonic area sounds recorded along with the carotid artery pulse (fig. 3) demonstrated that the split was paradoxical, i.e., aortic closure followed pulmonic. The second component of the second sound, preceding the carotid incisura by 0.02 second, represented aortic closure, and the first component was inscribed at the time of pulmonic closure. In the curve recorded during cardiac catheterization, the right ventricular pressure rise began 0.04 second earlier in the anomalous excitation cycles (fig. 4). Finally, it is observed in the simultaneous electrocardiogram and carotid artery pulse that the $P\text{-}CA_a$ was 0.02 second briefer and $P\text{-}CA_i$ 0.04 second shorter during WPW cycles. A similar tendency was noted in the onset of intrafemoral pressure (fig. 4). These observations are summarized in table 1.

These events indicated that with WPW conduction, the early activated right ventricle contracted and ejected prematurely. These conclusions were supported by the early right ventricular pressure rise recorded during catheterization and by phonocardiograms and carotid pulses, which establish the fact of early pulmonic closure, the latter event preceding aortic closure during anomalous excitation. Since the onsets and incisuras of the carotid pulse and intrafemoral pressure were also earlier at this time, it seems likely that the left ventricle was at least partly activated in an anomalous manner from the right side.

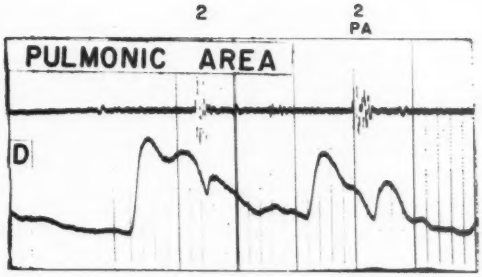

Figure 3

Case 1. The second beat is of the WPW type and pulmonic closure precedes the carotid incisura, indicating paradoxical splitting.

Table 2

Data for Case 2. (G. D., 47-year-old woman)

	WPW	Normal
Electrocardiogram		
P-R, second	0.13	0.18
QRS	0.14	0.09
P-S	0.27	0.27
Phonocardiogram		
P-S1, second	0.26	0.26
$P\text{-}S2_a$	0.52	0.56
$P\text{-}S2_p$	0.60	0.60
Mechanical events		
$P\text{-}CA_a$, second	0.27	0.27
$P\text{-}CA_i$	0.55	0.58
$CA_a\text{—}CA_i$, second	0.28	0.31

Abbreviations: P-R, onset of P to onset of R. P-S, onset of P to end of S wave. P-S1, onset of P to main deflection of first sound. $P\text{-}S2_a$ onset of P to aortic closure sound. $P\text{-}S2_p$ onset of P to pulmonic closure sound. $P\text{-}CA_a$ onset of P to carotid pulse upstroke. $P\text{-}CA_i$, onset of P to carotid pulse incisura. $CA_a\text{—}CA_i$, carotid pulse upstroke to carotid incisura.

Case 2

G. D. was a 47-year-old woman in whom the WPW syndrome was diagnosed during routine electrocardiography. She had been in good health but had experienced on occasion short flurries of rapid heart action. Physical examination was unremarkable except for a faint ejection murmur heard at the pulmonic area.

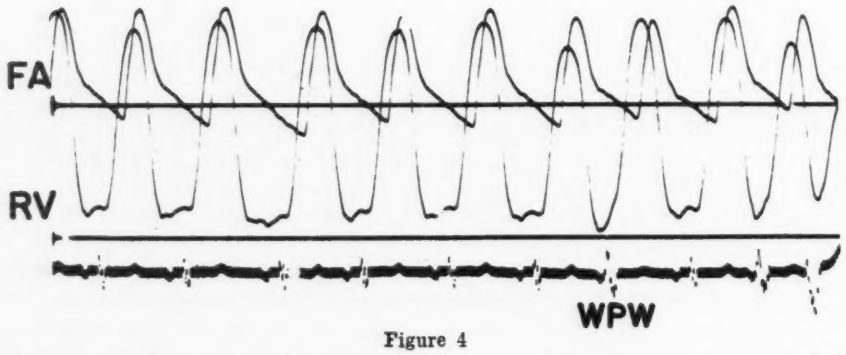

Figure 4

Case 1. Cardiac catheterization strip. The right ventricular pressure rise occurs 0.04 second earlier with the WPW beat than with the normal beats. The time lines do not photograph. FA: femoral artery. RV: right ventricle.

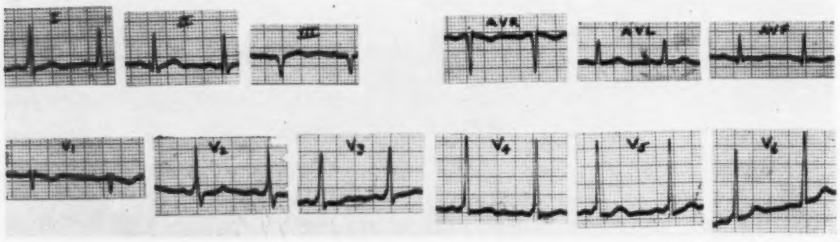

Figure 5

Case 2. Twelve-lead electrocardiogram showing WPW conduction, type A.

The electrocardiogram shown in figure 5 indicated WPW conduction. The precordial R waves were tall from V_2 to V_6 (type A). But this type of conduction was unstable and normal beats could be induced during Valsalva straining or on deep inspiration. As WPW beats reappeared in figure 6, the second sound became broadly split. The position of the components with reference to the carotid incisura indicated that aortic closure continued to precede pulmonic closure. Moreover, the intervals from P to aortic closure and to carotid incisura were 0.03 to 0.04 second shorter during WPW conduction. Also the descending limb of the carotid pulse was steeper and the interval from upstroke to incisura was briefer. These observations, summarized in table 2, suggested that during WPW conduction, left ventricular systole was completed earlier. The events on the contralateral side remained unchanged.

Case 3

M. F. was a 29-year-old patient with a history of paroxysmal atrial tachycardia. She had an apical diastolic rumble and the clinical diagnosis of mitral stenosis and WPW syndrome. Figure 7, right, is a 4-lead electrocardiogram recorded during anomalous excitation. The P-R interval was 0.10 second and the QRS was 0.12 second. Delta deformities were present in leads I and CR_4. The electrocardiogram on the left, recorded 2 months later, was essentially normal.

Phonocardiograms were recorded during both types of excitation (fig. 8). There was no essential difference between the normal (upper) record and the WPW (lower) record. The measured intervals are assembled in table 3. The deflection following the second sound in both records was an opening snap. This interpretation was further supported by the presence of a similar sound in the apical phonocardiogram, where it initiated a diastolic murmur.

In this case it would appear that anomalous excitation had no mechanical counterpart.

Phonocardiograms and pulses were available during WPW excitation alone in nine

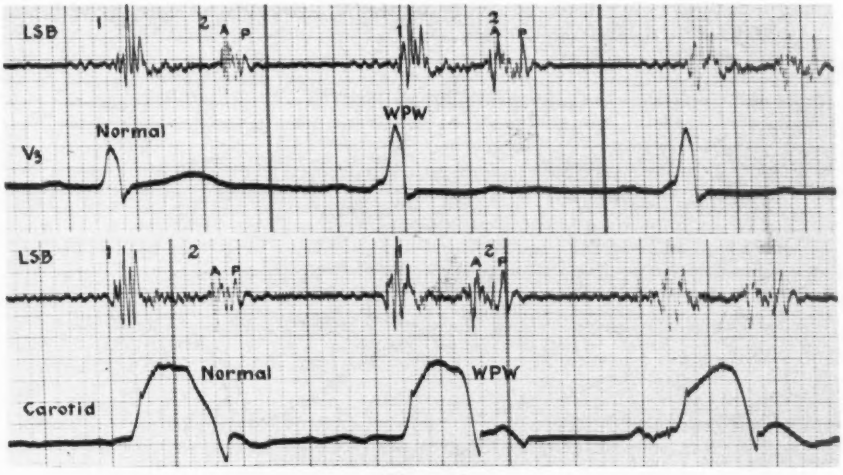

Figure 6

Case 2. As WPW beats reappear, the second sound splits widely due to earlier aortic closure. Note changes in the form of the carotid pulse, the incisura appearing early during WPW. The sound deflections have been retouched for clarity.

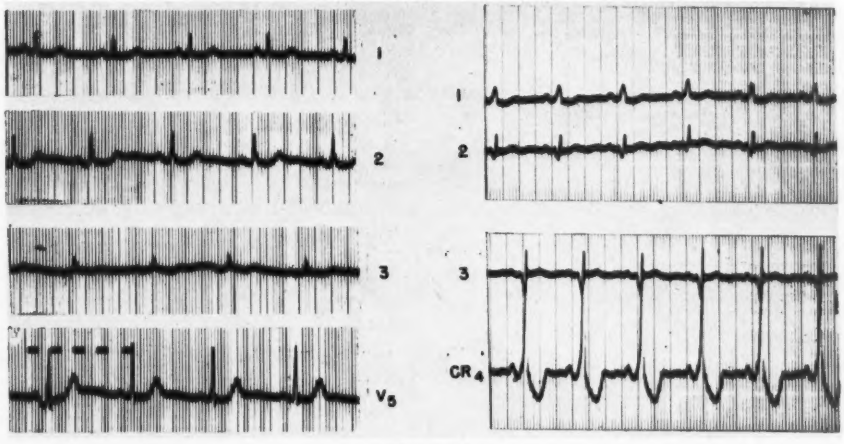

Figure 7

Case 3. The electrocardiogram on the right was recorded during WPW excitation, and the record on the left, made 2 months later, shows normal activation.

patients. In six of these patients the intervals from onset of the P wave to the time of the first and second heart sounds, and to the upstroke and incisura of the carotid were not remarkable, and in five of them, the first sound was not split while the second sound was either pure or split by less than 0.04 second.

The three other cases were considered separately and their data was summarized in table 4. They were similar in that pulmonic closure was delayed by 0.06 to 0.08 second (figs. 9 and 10). Splitting of this degree was not normally observed in phonocardiograms recorded with the chest held in mid or full expiration. In addition, there was splitting of the first sound in each instance at the left sternal border. The first sound was not nor-

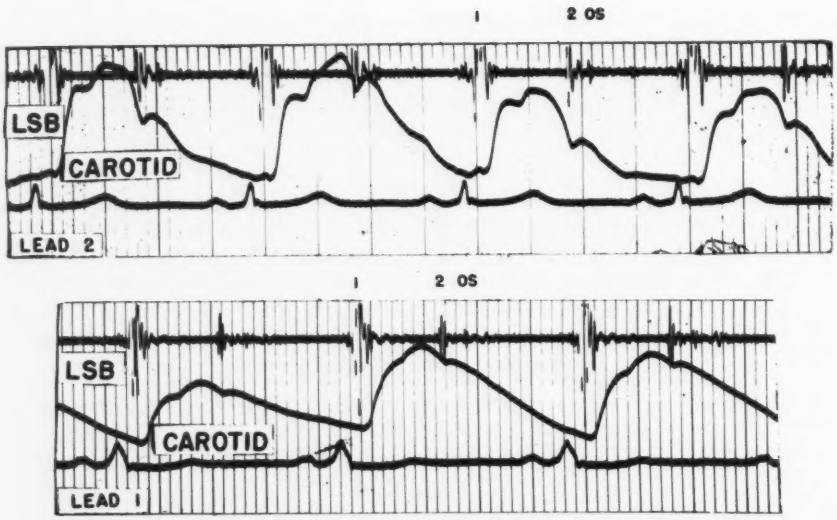

Figure 8

Case 3. Electrocardiogram, phonocardiograms, and carotid pulse during WPW conduction (lower record) and during normal conduction (upper record). There are no significant changes in the sounds or in the carotid events.

Table 3

Data for Case 3. (M. F., 24-year-old woman)

	WPW	Normal
Electrocardiogram		
P-R, second	0.10	0.16
QRS	0.12	0.06
P-S	0.22	0.22
Phonocardiogram		
P-S1, second	0.20	0.20
P-S2	0.56	0.56
Mechanical events		
$P\text{-}CA_2$, second	0.24	0.24
$P\text{-}CA_1$	0.58	0.58

Abbreviations: P-R, onset of P to onset of R. P-S, onset of P to end of S wave. P-S1, onset of P to main deflection of first sound. P-S2, onset of P to main deflection of second sound. $P\text{-}CA_2$, onset of P to carotid pulse upstroke. $P\text{-}CA_1$, onset of P to carotid pulse incisura.

mally split in excess of 0.03 second although separation of first sound components may have been simulated by atrial gallops and by ejection sounds. Although the patient illustrated in figure 9 was hypertensive and an ejection sound could not be excluded in that instance, the coexistence of delayed pulmonic closure in each sample suggests that the mitral and tricuspid sounds had become separated and that right ventricular contraction occurred late. In the one case of this group in which a 12-lead electrocardiogram was available, the precordial configuration was that of type A WPW (fig. 10), but the carotid pulse intervals did not suggest early ejection on the left side. In fact in this subject, and in W.B., the carotid upstrokes and incisuras were 0.02 to 0.03 second later than the mean of a control group, suggesting the possibility that activation was actually delayed on this side.

Discussion

The data presented here have been diverse. Study of the phonocardiogram and carotid pulse in seven patients with WPW furnished no evidence of ventricular asynchrony. Five patients with WPW electrocardiograms did exhibit anomalies of ventricular contraction. It is apparent from the evidence in two cases that during anomalous excitation, either ventricle may initiate or complete its contraction prematurely, and mechanical events on the opposite side may also be early. From three

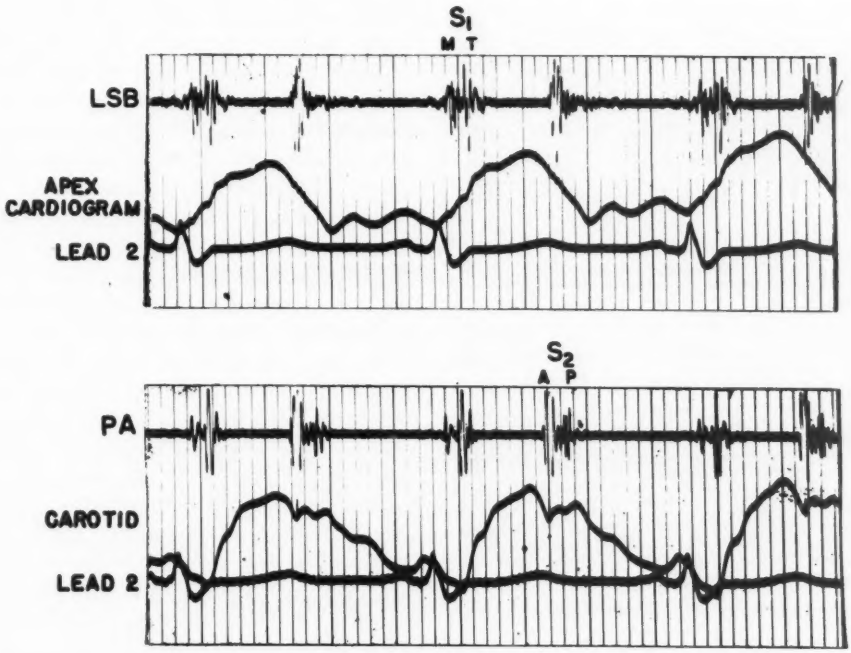

Figure 9

Case 4. Note broad splitting of first and second sounds and the delayed pulmonic closure evident in curves from the left sternal border and pulmonic areas.

Table 4

Data for Cases 4, 5, and 6

Patient Case	J. G. 4.	F. T. 5.	W. B. 6.	Normal controls (12) Mean	 S. D.
Electrocardiogram					
P-S, second	0.30	0.26	0.26	0.24	0.015
Phonocardiogram					
P-S1$_m$, second	0.23	0.24	0.23	0.23	0.015
P-S1$_t$	0.27	0.30	0.30		
P-S2$_a$	0.57	0.60	0.62	0.57	0.017
P-S2$_p$	0.64	0.67	0.68		
Mechanical events					
P-CA$_s$, second	0.30	0.32	0.32	0.29	0.015
P-CA$_i$	0.59	0.62	0.63	0.60	0.016

Abbreviations: P-S, onset of P to end of S wave. P-S1$_m$, onset of P to mitral closure. P-S1$_t$, onset of P to tricuspid closure. P-S2$_a$, onset of P to aortic closure. P-S2$_p$, onset of P to pulmonic closure. P-CA$_s$, onset of P to carotid pulse upstroke. P-CA$_i$, onset of P to carotid pulse incisura.

other cases in this study it also appears that during anomalous excitation, contraction was delayed, especially on the contralateral side, but possibly on both sides.

No single formulation is likely to explain all the observations presented here. When contraction is completly unaffected, it would seem that the electrical prematurity is of limited consequence and that the normal order of ventricular activation has been maintained. This would be most likely to occur when there has been no impairment of transmission

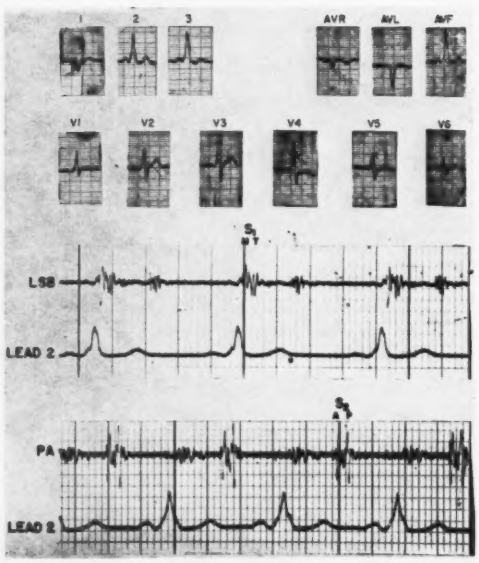

Figure 10

Case 5. The 12-lead electrocardiogram is typical of type-A WPW. There is broad splitting of first and second heart sounds and delayed pulmonic closure in tracings from the left sternal border and pulmonic areas.

through the atrioventricular node and when the anomalous entry is at a point relatively distant from ready access to the specialized conduction system. Such a situation might exist if the pathway entered the ventricle anterobasally or posterobasally and subepicardially. In spite of the early inscription of a delta wave, propagation would be slow and the area of delta activated myocardium would be limited by the timely appearance in the normal depolarization wave. With most of the myocardium remaining in the control of the specialized tissue as it were, mechanical events would be unaltered. Case 3 appears to have behaved in this manner.

When mechanical evidence for prematurity is present, it may be supposed that the propagation of the anomalous impulse is favored by a long transmission time through the atrioventricular node, and the entrance of the anomalous impulse in proximity to specialized conduction tissue. This site could be anywhere near the atrioventricular node or in the septum. Such a situation seems to have existed in case 1 in which anomalous excitation caused early contraction in both ventricles. Figure 2, in which WPW and "normal" complexes alternate, is instructive for a number of reasons. It shows in the "normal" complexes that atrioventricular conduction was actually prolonged, since it is 0.18 second in a 9-year-old girl. It is curious that any sort of normalization should occur with a P-R interval of this duration, since one would expect all beats to remain of the WPW type. The morphology of the "normal" beats indicates that activation actually begins anomalously, i.e., one still sees a delta wave, but that in these beats conduction through the anomalous pathway seems to be depressed and impulses over it reach the ventricle only shortly before those from the specialized conduction system, which activates most of the myocardium and inscribes an almost normal QRS complex. Functionally then, in these beats the anomalous pathway is inconsequential, there are no mechanical abnormalities other than the soft first sound, which would be expected with a long P-R interval, and the situation is very similar to that outlined for case 3.

This situation contrasts sharply with the obviously deformed QRS complexes of the WPW beats. The mechanical abnormalities attending these beats are quite different from those described by Prinzmetal in his experimental study.[7] Prinzmetal's cine-film data suggested that during anomalous excitation, a small area in the ventricle precontracts. This contraction is too weak to open the semilunar valve, and also probably too weak to close the atrioventricular valve. Most of the ventricle then contracts normally and the total duration of systole is prolonged. In the WPW beats of case 1, however, the precontracting right ventricle exhibits a sharp early pressure rise as indicated in the cardiac catheterization curve. In left sternal border phonocardiograms the first heart sound appears early after a very short P-R interval and is therefore loud, in contrast to the faint sound inscribed after the long P-R interval

of the "normal" beats. Pulmonic closure occurs before aortic, resulting in a paradoxical split of the second sound, and the total duration of right ventricular systole is not prolonged. Moreover, the data suggest that systole also begins and ends earlier on the left side as evidenced by the shorter P-S interval of the electrocardiogram in WPW beats, and by the shorter P to carotid upstroke and incisura intervals. In view of the broad, deformed QRS complex in these beats, the spread was probably transmyocardial from right to left. By virtue of the very early appearance of the activation wave in the ventricle with WPW as compared to "normal" beats, the left ventricle is activated early even though this activation probably occurs in a manner similar to that of left bundle-branch block.

In case 2 both ventricles began their contraction on time in WPW beats when compared with normal beats. With WPW beats, the second sound became broadly split due to early aortic closure. Pulmonic closure time was unchanged. The form of the carotid pulse suggests that the normal beats have a longer systole duration than WPW beats and these considerations imply that left ventricular systole is more quickly terminated during the anomalous excitation. The reason for this is not clear. Since the WPW beats were induced by holding the breath after a full expiration, it is possible that the shortening of left ventricular systole was due to the effect of the respiratory maneuver on stroke volume. A full expiration, however, increases intrathoracic pressure and promotes pulmonary venous return. Therefore it usually acts to augment stroke volume in the left ventricle rather than to reduce it.

In the final examples activation was delayed on the right or contralateral side, although no prematurity could be found on the left, presumably the side of the anomalous focus. In Ferrer's experience delay was present on both sides.[11] This situation could not be definitely established here. In two of the three cases in this category, however, the carotid upstrokes and incisuras were 0.02 to 0.03 second later than the mean of a control group in which the standard deviation was small, but this can only be regarded as suggestive. If it were the case, one would have to agree with Ferrer that both ventricles are activated in a transmyocardial manner from a high basilar focus in the left ventricle. What has happened to the atrioventricular node and the normal conduction pathways under these circumstances? Their role seems to be obscure. Patient F. T., who belongs in this group, has a typical type A WPW electrocardiogram. He has had anomalous excitation for 14 years, and a normal electrocardiogram has never been recorded. Strenuous efforts were made to produce normal conduction, including hyperventilation, Valsalva maneuvers, 1.6 mg. of atropine intravenously with recordings in both supine and standing positions, 1.0 Gm. of procaine amide intravenously, and 5.0 Gm. of quinidine by mouth. None of these expedients produced normal complexes. It is a distinct possibility that in such a case, the atrioventricular node is nonfunctioning and that the anomalous pathway is the sole avenue of excitation of the ventricles.

Summary

The mechanical consequences of anomalous atrioventricular excitation were studied in 12 patients by means of phonocardiograms, carotid pulse tracings, and in one instance, by data from cardiac catheterization. Three of these patients were also observed during normal conditions so that they supplied their own control data.

In five instances mechanical anomalies were detectable as a consequence of the electrocardiographic abnormality. These anomalies were complex and consisted in one case of early onset and completion of ejection on both sides, and in another case of early completion on the left side. In three instances there was late activation on the contralateral side and possibly on the homolateral side as well.

The remaining cases exhibited no such abnormalities by the methods studied, and in one subject this is illustrated with records

made during both anomalous and normal conduction.

The literature pertaining to this problem is critically reviewed, and an attempt is made to interpret both the previous and the present observations. The divergent nature of the observations suggests that the effect of anomalous excitation on the mechanics of the heart is the resultant of a number of variables, including the transmission time through the atrioventricular node and the site of entry of the anomalous focus.

It is possible that the atrioventricular node does not function in some cases in which Wolff-Parkinson-White conduction is always present and it is not possible to induce normal beats with drugs, exercise, or respiratory maneuvers.

Acknowledgment

The authors wish to express their appreciation and indebtedness to Dr. David A. Rytand, whose interest and foresight in recording most of these records have made this study possible.

References

1. Wolff, L., Parkinson, J., and White, P. D.: Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. Am. Heart J. 5: 685, 1930.
2. Wolferth, C. C., and Wood, F. C.: The mechanism of production of short P-R interval and prolonged QRS complexes in patients with presumably undamaged hearts. Am. Heart J. 8: 297, 1933.
3. Holzmann, M., and Scherf, D.: Über Electrokardiogramme mit verkurzter Vorhof-kammer-distanz und positiven P-zaken. Ztschr. klin. Med. 121: 404, 1932.
4. Butterworth, J. S., and Poindexter, C. A.: Short P-R interval associated with a prolonged QRS complex. Arch. Int. Med. 69: 437, 1942.
5. Wolff, L.: Anomalous atrioventricular excitation. Circulation 19: 14, 1959.
6. Harnischfeger, W. H.: Hereditary occurrence of the pre-excitation (WPW) syndrome with re-entry mechanism and concealed conduction. Circulation 19: 28, 1959.
7. Prinzmetal, M., Kennamer, R., Corday, E., Osborne, J. A., Fields, J., and Allen Smith, L.: Accelerated Conduction. The Wolff-Parkinson-White Syndrome and Related Conditions. New York, Grune & Stratton, Inc., 1952.
8. Pick, A., and Katz, L. N.: Disturbances of impulse formation and conduction in WPW. Am. J. Med. 19: 759, 1955.
9. Bandiera, G., and Antognetti, P-F.: Ventricular precontrasting area in the WPW syndrome. Circulation 17: 759, 1955.
10. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: The potential variations of the thorax and esophagus in anomalous atrioventricular excitation (WPW) syndrome. Am. Heart J. 29: 281, 1945.
11. Ferrer, M. I., Harvey, R. M., Weiner, H. M., Cathcart, R. T., and Cournand, A.: Hemodynamic studies in 2 cases of WPW syndrome with paroxysmal atrioventricular nodal tachycardia. Am. J. Med. 6: 725, 1949.
12. Samet, P., Mednick, H., and Schwedel, J. B.: Electrokymographic studies of electrical and mechanical asynchronism. Electrokymography, Proceedings of the First Conference, Sponsored by the National Heart Institute, May 25-26, 1950.
13. Dack, S., Paley, D. H., and Brahms, S. S.: The electrokymogram in WPW syndrome. Am. Heart J. 41: 437, 1951.
14. Moia, B., and Inchauspe, L. H.: Sobre un case de P-R corton con QRS ancho y mellado presentando asincronismo ventricular. Rev. argent. de cardiol. 5: 114, 1938.
15. Cossio, P., Berconsky, I., and Kreutzer, R.: P-R acortado con QRS ancho y mellado, tipo bloqueo de rama o blaqueo intraventricular de menor grado. Rev. argent. cardiol. 2: 411, 1936.
16. Scherf, D., and Schonbrunner, E.: Beitrage zum Problem der verkurzten Vorhofkammerleitung. Ztschr. klin. Med. 128: 750, 1935.
17. Kossmann, C. E., and Goldberg, H. H.: Sequence of ventricular stimulation and contraction in a case of anomalous atrioventricular excitation. Am. Heart J. 33: 308, 1947.
18. Öhnell, R. F.: Pre-excitation; a cardiac abnormality. Acta med. scandinav., Suppl. 152: 1, 1944.
19. Leatham, A.: Symposium on cardiovascular sound. Circulation 16: 418, 1957.

Aortic Pressures during Closed-Chest Cardiac Massage

By Victor Gurewich, M.D., Arthur A. Sasahara, M.D., James S. Quinn, M.D., Catherine J. Peffer, M.D., and David Littmann, M.D.

RESUSCITATION by cardiac massage through the closed chest has been described recently by Kouwenhoven and associates.[1] This technic consists of applying firm, rhythmic pressure to the lower sternum, thus compressing the heart between it and the spine. Based on exhaustive animal experiments, this method was instrumental in the effective cardiac resuscitation of 20 patients reported by the authors. Three of these cases were observed to be in ventricular fibrillation.

The present report concerns an episode of ventricular fibrillation during retrograde left heart catheterization that afforded an opportunity to obtain direct aortic pressure measurements while closed-chest cardiac compression was being performed.

Case Report

R. N., a 36-year-old white man, was admitted for evaluation of incapacitating episodes of squeezing anterior chest pain. No abnormalities were found on physical examination. The results of examination of the blood and urine were entirely within normal limits. Serial electrocardiograms, a 100-trip, two-step exercise tolerance test, and roentgenologic examination of the chest and gastrointestinal tract yielded normal findings.

Since the patient's symptoms suggested angina pectoris, it was decided to perform a coronary angiogram in order to clarify the puzzling clinical picture.

At 7:30 a.m. the patient received meperidine, 75 mg. intramuscularly, and secobarbital, 100 mg. by mouth. At 8:15 a.m. a loop-end, polyethylene catheter was introduced into the femoral artery and passed in retrograde direction up the aorta by the method described by Williams et al.[2] The electrocardiogram and direct arterial pressures were monitored continuously with a multichannel recorder.* As the catheter was being passed into the ascending aorta to the region of the sinus of Valsalva, the patient experienced a brief episode of burning substernal pain unassociated with electrocardiographic changes. An injection of 5 ml. of 90 per cent diatrizoic acid (Hypaque) was then made into the end of the catheter to test sensitivity and for purposes of visualization. The catheter, which holds approximately 4 ml., was noted to be located just above the aortic valves. Another 1 ml. was introduced in order to define more clearly the loop-end.

At this time, 8:30 a.m., the patient complained of severe, substernal burning pain, almost immediately lost consciousness, and had a generalized convulsion. Ventricular fibrillation was observed on the monitor and the catheter was promptly withdrawn below the diaphragm. The patient remained cadaveric in appearance despite attempts at resuscitation that included immediate sternal pressure and repeated, ineffective attempts at transthoracic defibrillation with a 150-volt internal defibrillator followed by application of an external electric cardiac pacemaker (fig. 1, no. 2). After an estimated 5 to 8 minutes had elapsed, closed-chest cardiac compression according to the method described by Kouwenhoven et al.[1] was started.

Blood pressures of 80/40 mm. Hg (fig. 1, nos. 3 and 4) were immediately obtained from the catheter in the abdominal aorta and the patient's color appeared to improve. He had been ventilated continuously first by mouth-to-mouth respiration and within 10 minutes by intubation and intermittent positive pressure with oxygen. Procaine amide hydrochloride, 500 mg., was given intravenously while external massage was being carried on, but the arrhythmia persisted.

At 9:10 a.m., because of persistent fibrillation, after approximately 30 minutes of effective circulation, external massage was discontinued and a thoracotomy was performed by Dr. Martin Litwin. As the pericardium was being incised, the rhythm changed spontaneously to an inconstant ventricular tachycardia. Direct manual massage of the exposed heart was begun; this produced arterial pressures of approximately 100/65 mm. Hg (fig. 1, no. 5) recorded from the catheter in the abdominal aorta. Adequate, spontaneous cardiac contractions developed after a few minutes of cardiac massage. At 9:20 a.m., the rhythm changed to a nodal tachycardia and the chest was closed. After a few short runs of ventricular tachycardia, a fairly stable sinus rhythm developed. An adequate blood pressure was maintained with the aid of small doses of metaraminol (Aramine).

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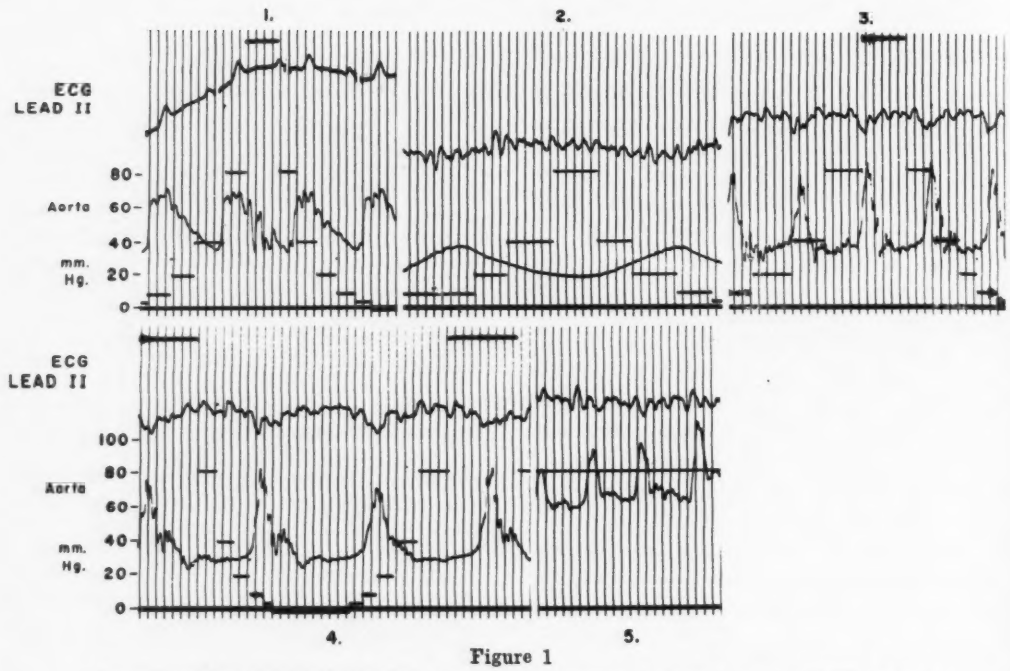

Figure 1

Representative segments of tracing showing the electrocardiogram above and intraluminal aortic pressure below. The vertical time-lines are at 0.1-second intervals. 1. Tracing prior to onset of ventricular fibrillation showing normal sinus rhythm and normal ventricular beats with corresponding pressures in the ascending aorta. 2. Following onset of ventricular fibrillation with baseline pressures before cardiac massage. 3 and 4. Arterial pressure recordings from the abdominal aorta during closed-chest cardiac massage at rates of 75 and 50 beats per minute. The electrocardiogram shows persistent ventricular fibrillation. 5. Pressure recording during open-chest manual massage.

Hypothermia was instituted in order to limit the anoxic brain damage, but despite all measures the patient never regained consciousness and died at 1:45 a.m. the following morning, following another bout of ventricular fibrillation.

Postmortem examination revealed scattered, focal hemorrhagic areas seen on cross-section of the myocardium, which were interpreted to be injuries sustained during direct, manual cardiac massage. No other abnormalities were found. There were no injuries of the thoracic cage, and there was no evidence of coronary artery disease. It is assumed, though there is no proof, that the cardiac arrhythmia resulted from a reaction to the contrast substance.

Discussion

Direct arterial pressure recordings in this case illustrate that rhythmic, manual compression of the lower sternum can produce a substantial blood pressure in the distal aorta during ventricular fibrillation. Coincident improvement in the patient's color suggested that this was associated with a significant peripheral flow of oxygenated blood. A pressure of 80/40 mm. Hg (fig. 1, nos. 3 and 4) was immediately obtained and maintained thereafter without difficulty throughout the period of closed-chest massage. This level compared favorably with the patient's premorbid, resting arterial pressure of 70/40 mm. Hg (fig. 1, no. 1), but was slightly less than the pressures obtained by open-chest, manual cardiac massage, which averaged around 100/70 mm. Hg (fig. 1, no. 5).

In all probability, the failure to revive this patient was due to the prolonged period of hypotension. External application of adequate countershock current may well have termi-

nated the fibrillation and restored normal sinus rhythm with or without the use of the external pacemaker.

It is noteworthy that no injuries to the thoracic cage were found at postmortem examination. One of the foreseeable complications of vigorous transthoracic massage is that of rib fractures with accompanying laceration of the underlying heart, great vessels, and other organs. In all likelihood, the elasticity of the thorax will have some influence on the safety and efficacy of this technic, although one of the successful resuscitations reported by Kouwenhoven et al. was in an 80-year-old woman.[1]

The attractive features of closed-chest cardiac compression include its simplicity, ease of application, and general applicability regardless of place and regardless of whether the heart is in standstill or fibrillation. Valuable time may be gained through this method for obtaining other resuscitative equipment, such as an electric external pacemaker and defibrillator.

It is apparent from this case that substantial blood pressures, equal to the patient's own resting levels and slightly less than those produced by direct cardiac massage, can be obtained by this method. It appears likely that this is the procedure of choice in the treatment of cardiac arrest occurring outside the operating room or where an external pacemaker or defibrillator is not immediately available.

Summary

A case of ventricular fibrillation is presented which occurred during retrograde left heart catheterization and preparation for aortography. Direct arterial pressures were recorded from a catheter in the abdominal aorta during closed-chest cardiac massage. These indicated that substantial blood pressures can be readily produced by this simple and practical method.

References

1. Kouwenhoven, W. B., Jude, J. R., and Knickerbocker, G. G.: Closed-chest cardiac massage. J.A.M.A. **173**: 1064, 1960.
2. Williams, J. A., Littmann, D., Hall, J. H., Bellman, S., Lambert, P. B., and Frank, H. A.: Coronary arteriography. II. Clinical experiences with the loop-end catheter. New England J. Med. **262**: 328, 1960.

Nothing will sustain you more potently than the power to recognize in your hum-drum routine, as perhaps it may be thought, the true poetry of life—the poetry of the commonplace, of the ordinary man, of the plain, toil-worn woman, with their love and their joys, their sorrows and their griefs.—Sir William Osler. *Aphorisms From His Bedside Teachings and Writings.* New York, Henry Schuman, Inc., 1950. p. 90.

Isolated Incompetence of the Pulmonic Valve

By BEN O. PRICE, M.D.

IN 1936 Kissin[1] reviewed the literature and described the clinical and pathologic picture of isolated incompetence of the pulmonic valve. His study was based upon an analysis of autopsy protocols, and it remained for Kezdi et al.,[2] in 1955, to report the first case diagnosed during life. To date 13 cases of isolated incompetence of the pulmonic valve have been reported in the English literature.

It is the purpose of this paper to report two additional patients diagnosed during life, and to summarize the data available on these 15 cases.

Case Reports

Case 1

A. A., a 60-year-old woman, was first told that she had a heart murmur at the age of 15. During the next decade she experienced two uncomplicated deliveries. At the age of 27 she was refused life insurance because of heart disease. Her first cardiac symptoms developed at the age of 50, when she had an episode of rapid heart action, shortness of breath, and anxiety. In May 1957 she had moderately severe dyspnea on exertion. Other symptoms strongly suggested that emotional tension might be the major factor in production of the dyspnea.

Examination at that time revealed a blood pressure of 138/90. Abnormal physical findings were limited to the heart. The rhythm was regular and there were no thrills or abnormal pulsations. A grade-II systolic murmur and a grade-I harsh, diastolic murmur were best heard along the left sternal border in the third interspace. The first heart sound was split in the mitral area. An electrocardiogram was interpreted as right ventricular hypertrophy. Fluoroscopy demonstrated enlargement of the left atrium and very active pulsation of the hilar vessels.

At right heart catheterization on May 8, 1957, the pulmonary artery and right ventricular pressures were identical, and there was no evidence of a left-to-right shunt (table 1).

She was seen at the University of Arkansas Medical Center in May 1959, complaining of numbness and paresthesia of the arms and hands, insomnia, and shortness of breath on exertion. She stated that she had been taking digitalis for the past 2 years and had been able to work steadily, although occasionally she felt weak and dyspneic. Except for two episodes of pneumonia there was no history of infectious disease, rheumatic fever, or syphilis.

Positive physical findings again were limited to the heart. There were no palpable thrills and the rhythm was regular. A grade-II systolic murmur was best heard in the second left intercostal space parasternally, and a grade-III rough, crescendo-decrescendo, middiastolic murmur was heard in the same area. Routine laboratory studies were normal.

An electrocardiogram (fig. 1) showed sinus rhythm and right ventricular hypertrophy. Chest fluoroscopy confirmed the presence of active hilar pulsations and generalized cardiac enlargement, predominantly involving the right ventricle and pulmonary artery.

Right heart catheterization was repeated on August 26, 1959 (table 1).

Case 2

E. M., a 37-year-old Negro woman, was referred to the hospital for evaluation of hypertension. She complained of dyspnea on exertion and palpitation. At the age of 15, 3 months after the delivery of her first child, she developed dyspnea, orthopnea, and anasarca. She was told that she had a large heart and was given digitalis. After 8 months of convalescence she was asymptomatic and medications were discontinued.

During the next 10 years she had four more pregnancies, the first two being uncomplicated. Her fourth pregnancy was complicated by the appearance of hypertension. She remained asymptomatic, however, until the last trimester of her fifth pregnancy, when she developed shortness of breath with an inordinate amount of ankle edema. The labor, delivery, and postpartum period were uncomplicated. For the next 5 years she had minimal cardiac symptoms and was able to perform her housework with little limitation of activity. The antecedent history revealed that the patient's mother and father had died of hypertension.

Examination showed a moderately obese, alert Negro woman whose blood pressure ranged between 120/30 and 150/100 mm. mercury. Abnormal physical findings were limited to the heart, which was moderately enlarged to the left. There were no thrills and the rhythm was regular. A

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Table 1

Data on Two Patients

Position	RV	PA	BA	IVC	RA	SVC
A. A.: 5-8-57						
Pressure*	45/5	45/5	135/75	10/0	12/2	10/0
Per cent saturation	68	70	94	74	71	69
8-26-59						
Pressure	40/4	40/4	156/84	2†	2†	2†
Per cent saturation	66	62	96	73	69	66
E. M.: 6-6-57						
Pressure	20/0	—	124/85		3*	3*
Per cent saturation	68.5	—	94.5	75	68.5	68.5
4-28-60						
Pressure	45/0	43/0				
Per cent saturation						

*Millimeters of mercury.

†Mean pressure.

RV, right ventricle; PA, pulmonary artery; BA, brachial artery; IVC, inferior vena cava; RA, right atrium; SVC, superior vena cava.

grade-II systolic and a grade-II harsh, diastolic murmur were heard best in the third left intercostal space parasternally. A phonocardiogram demonstrated a rough, holosystolic murmur loudest over the pulmonic area, a distinct second sound at the pulmonic area, and a crescendo-decrescendo middiastolic murmur of low frequency and moderate intensity.

An electrocardiogram showed right ventricular hypertrophy (fig. 2). Chest fluoroscopy demonstrated a pulsating right hilar mass and moderate cardiac enlargement.

At right heart catheterization in June 1957 (table 1), the pulmonary artery was not entered for technical reasons. In April 1960, repeat right heart catheterization and angiocardiography were performed. The angiocardiogram demonstrated aneurysmal dilatation of the pulmonary arteries. Catheterization (table 1) demonstrated identical pressures in the pulmonary artery and right ventricle with mild systolic hypertension. The pulmonary wedge pressure was normal.

Comment

In both patients heart disease was diagnosed early in life, suggesting the presence of a congenital defect. While both patients have a limited exercise tolerance, neither has objective evidence of heart failure.

Review of Literature

The data of 15 cases diagnosed during life are summarized in table 2. Their ages ranged from 7 to 60 years, with a median of 24 years, and there were eight females and seven males. While nine patients had definite cardiac symptoms, six had complicating diseases that probably contributed to their symptoms. All patients free of cardiac symptoms were under 25 years of age; however, congestive failure did occur in patients who had other diseases.

In every case systolic and diastolic murmurs were heard over the second and third left intercostal spaces at the sternal border. In five cases a diastolic thrill was palpable. Phonocardiograms were described in six cases and all demonstrated murmurs of maximum intensity in middiastole. Five of these were definitely crescendo-decrescendo in character.

Electrocardiograms were reported as normal in four cases. Right ventricular hypertrophy or incomplete right bundle-branch block was diagnosed in seven cases. Low voltage and right axis deviation were each observed once.

Increased pulsation of the pulmonary vessels was the most outstanding roentgenographic finding, being present in every instance in which cardiac fluoroscopy was performed. Enlargement of the pulmonary artery and right ventricle was noted 10 and six times respectively.

Table 2

Isolated Incompetence of Pulmonic Valve—Cases Diagnosed During Life

Author and reference	Age and sex	X-ray				Electrocardiogram				Cardiac symptoms	Complicating disease	Systolic murmur	Diastolic murmur	Catheterization data				Alive	Dead	Autopsy	Diagnosis and autopsy findings
		Over-all heart size	Hilar dance	RVH	Large PA	Normal	RVH	RBBB	Incomplete RBBB					Cardiac index or cardiac output	RV, systolic/diastolic	PA, systolic/diastolic	PVR				
Kezdi[2], 1955	24 M	N	+	(−)	+	+				(−)	(−)	+	+	3.7	24/1	21/2		+			Pulmonic incompetence, congenital
Olesen[4], 1955	45 F	Lge	+	+	+			+		+	+	+	+	(3)	28/0	28/0		+			Gonorrheal pulmonic valvulitis
Ehrenhaft[5], 1955	14 M	Lge	0	+	+			+		+	(−)	+	+	(4.6)	50/7	27/10		+			Absence PV—(?) congenital
Ford[6], 1956	43 F	N	+	+	+		+			+	+	+	+	2.1	29/5	29/5			+	+	Bicuspid PV, congenital, pul. fibrosis, myocardial fibrosis
Morton[1], 1956	20 F	N	+	(−)	+			+		+	(−)	+	+	3.4	22/3	21/2		+			Pulmonic valve incompetence, (?) congenital
Segel[8], 1957	7 M	N	+	(−)	+				+	(−)	(−)	+	+		25/0	15/5		+			Pulmonic valve incompetence, congenital
Dickens[9], 1958	46 F	Lge	0	+	+	(−)				+	+	+	+	3.4	73/10	75/25	753.		+	+	Bicuspid pulmonic valve, pulmonary arteriolosclerosis
Lendrum[10], 1958	16 M	N	+	(−)	(−)				+	(−)	(−)	+	+		32/8	20/9		+			Pulmonic valve incompetence, congenital
Fish[12], 1959	51 M	N	+	(−)	(−)	+				+	+	+	+	2.3	34/5	34/5		+			Pulmonic valve incompetence, cause unknown
Kjellberg[13], 1959	9 F	N	0	(−)	(−)	+				(−)	(−)	+	+		32/8	22/4		+			Pulmonic valve incompetence, congenital
Kjellberg*, 1955	7 M	N	0	(−)	(−)	+				(−)	(−)	+	+		20/2	15/0		+			Pulmonic valve incompetence, congenital
Collins[14],* 1960	36 F	N	+	(−)	+	(−)				+	(−)	+	+	2.55	28/7	28/7		+			Pulmonic valve incompetence, congenital
Collins, 1960	16 M	0	0	+	0	0				(−)	(−)	+	+		48/8	22/8		+			Pulmonic valve incompetence, congenital
Price*, 1960	60 F	Lge	+	+	+		+			+	+	+	+		40/4	40/4		+			Pulmonic valve incompetence, cause unknown
Price*, 1960	37 F	Lge	+	+	+		+			+	+	+	+		45/0	43/0		+			Idiopathic dilatation of pulmonary artery and incompetence of pulmonary valve
Total	15																	13	2		

*, Phonocardiogram; +, yes; (−), no; 0, unknown; N, normal; Lge., enlarged; RVH, right ventricular hypertrophy; CI, cardiac index; PVR, peripheral vascular resistance in dynes per cm.$^{-5}$; RBBB, right bundle-branch block; PA, pulmonary artery; PV, pulmonary valve; RV, right ventricle.

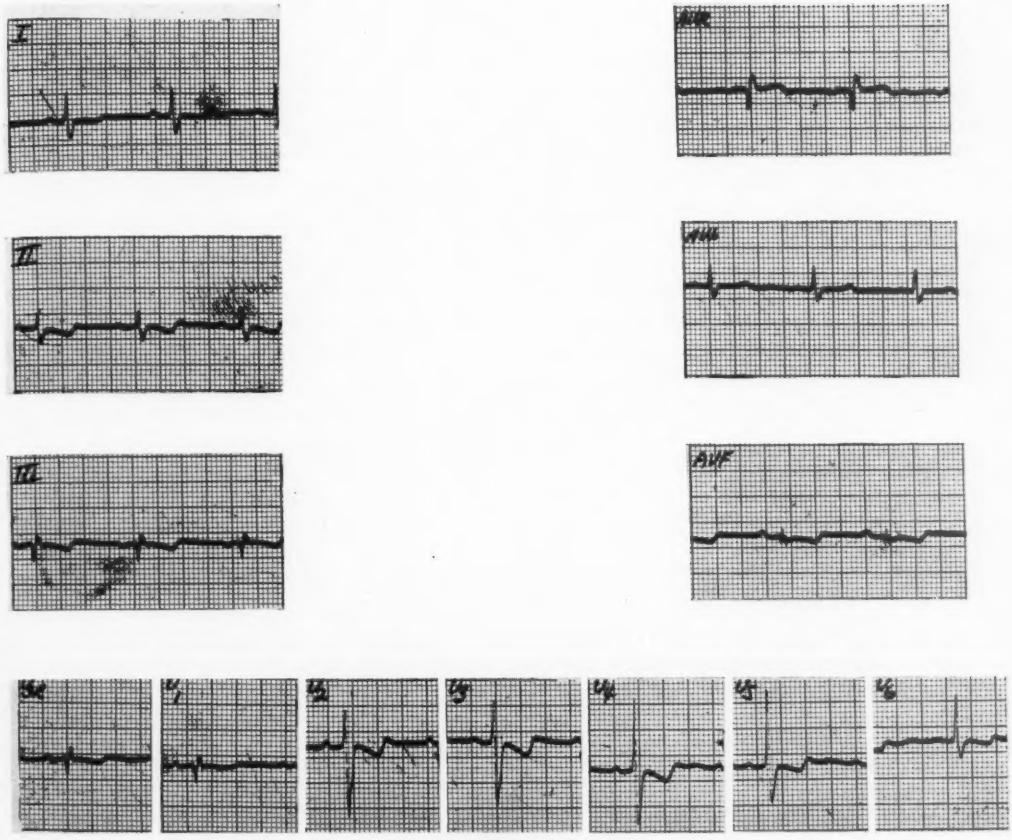

Figure 1

Electrocardiogram (case 1) showing sinus rhythm and right ventricular hypertrophy.

Right heart catheterization was performed in all cases. Nearly identical diastolic pressures in the right ventricle and pulmonary artery were observed in every instance. Several authors emphasized the diagnostic significance of a steeply sloping dicrotic limb in the pulmonary artery pressure curve. When cardiac output was determined, the values were moderately low.

At the time of report, 13 patients were alive and two were dead. Autopsy of both these patients demonstrated congenital deformities of the pulmonic valve that were adequate to produce the insufficiency observed clinically. While diagnoses in the other cases are presumptive, the early ages when heart disease was discovered suggests a congenital etiology.

Discussion

In 1936 Abbott[3] demonstrated that isolated incompetence of the pulmonic valve comprised 0.8 per cent of 1,000 consecutive cases of congenital heart disease. The data presented here demonstrate that this lesion, while rare, has a distinct clinical picture. The diagnosis should be considered in patients with a low-pitched, middiastolic murmur over the base of the heart who have evidence of right heart enlargement. Cardiac fluoroscopy is helpful and may demonstrate enlarged, vigorously pulsatile pulmonary arteries and right ventricular enlargement. The electrocardiogram

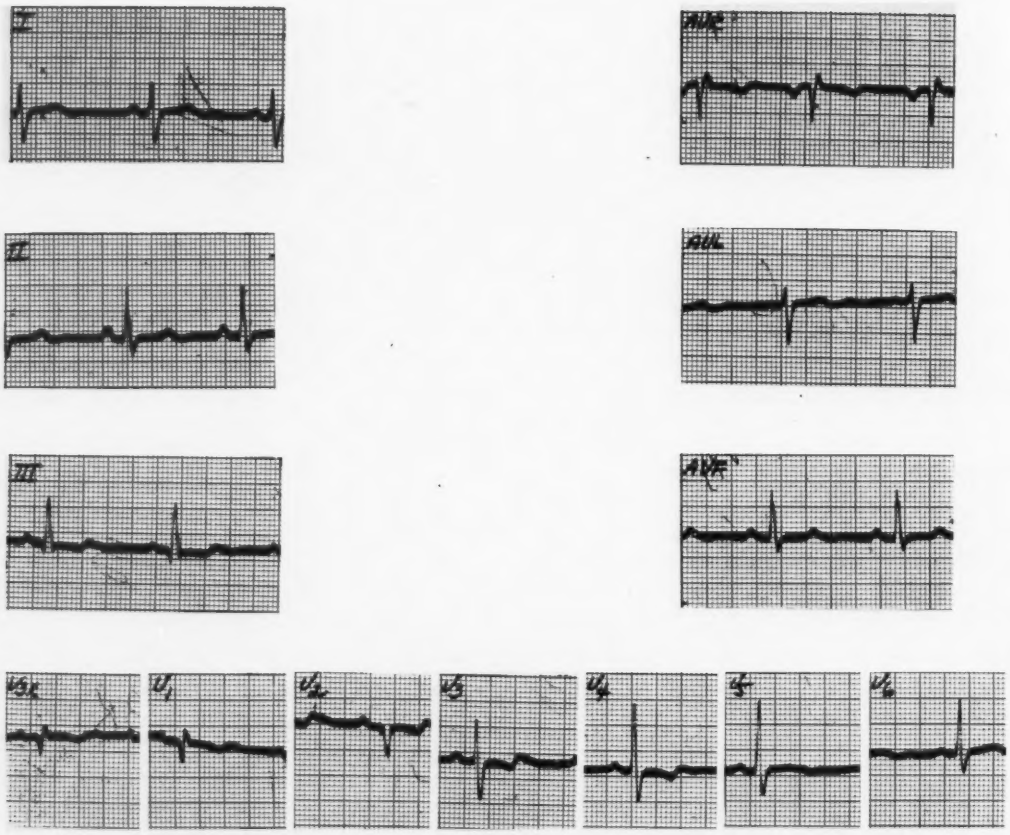

Figure 2

Electrocardiogram (case 2) showing right ventricular hypertrophy.

is not distinctive and may be normal. Frequently right bundle-branch block or right ventricular hypertrophy is seen.

The clinical impression can be confirmed by right heart catheterization. The diastolic pressure in the pulmonary artery should be essentially the same as in the right ventricle. A late or absent dicrotic notch and a steeply sloping dicrotic limb are characteristic features of the pulmonary artery pressure curve.

Numerous authors[5, 6, 12, 14–17] have been concerned with the hemodynamic effects of pulmonic insufficiency. Working with dogs in whom this lesion was produced surgically, Barger, Roe, and Richardson[15] concluded, "pulmonic insufficiency has remarkable little effect on work tolerance or atrial pressure even after months of daily strenuous exercise." Fowler and Dushane[16] demonstrated right ventricular dilatation and a fall in resting cardiac output in eight dogs that survived 11 to 18 months after surgical excision of the pulmonary valve. They concluded that pulmonic insufficiency was not an entirely benign lesion. Blount, McCord et al.,[17] reported five patients who developed pulmonic insufficiency after corrective surgery for pulmonic valvular stenosis. In all cases the heart size increased postoperatively. While no hemodynamic alterations were observed, the follow-up time was relatively short.

The auscultatory findings in isolated pulmonic insufficiency are of interest. A systolic

and a diastolic murmur were invariably heard along the upper left sternal border. The second sound was usually of normal intensity and occasionally was split. Phonocardiograms show an interval between the second sound and the onset of the murmur which is of relatively low frequency and has a crescendo-decrescendo quality. The cause of the mid-diastolic murmur is not known. Segel et al.,[8] stated that it was "similar in mechanism to the apical middiastolic murmur associated with aortic regurgitation." Since the maximum intensity of the murmur occurs when the right ventricular pressure is lowest, one may speculate that the murmur is produced by rapid filling of the dilated right ventricle.

Our data and that collected from the literature clearly indicate that isolated pulmonic insufficiency is not an entirely benign disease in the human being. The presence of symptoms, evidence of right ventricular enlargement, and low resting cardiac output confirm that isolated incompetence of the pulmonic valve does interfere with normal cardiac function.

As one might predict, any pathologic process that tends to increase pulmonary blood flow or pulmonary artery pressure will further compromise right ventricular function. This was beautifully demonstrated by the case of Smith et al.,[11] in which heart failure occurred in a fetus who had no pulmonic valve. The case reported by Ford et al.,[6] of pulmonary hypertension developing in a 43-year-old woman affords an example of right ventricular failure occurring with a complicating disease. The dilatation and hypertrophy of the right ventricle and pulmonary outflow tract are best explained by the increase in stroke volume produced by incompetence of the pulmonic valve. These changes may be expected to decrease cardiac reserve to the point that failure of the right ventricle will occur when it is subjected to increased work loads.

Summary

Two cases of isolated incompetence of the pulmonic valve diagnosed during life are reported and a review of the literature is presented.

The diagnosis should be suspected in patients with a basal diastolic murmur and right ventricular enlargement who have no evidence of other cardiac valvular disease.

The characteristic murmur associated with isolated incompetence of the pulmonic valve appears to be related to filling of the dilated right ventricle.

The diagnosis can be confirmed clinically by right heart catheterization.

The lesion is not benign in the human being, and right ventricular failure may be precipitated when complicating diseases are present.

Acknowledgment

The author is deeply grateful to the Memorial Diagnostic Heart Service Association, Kansas City, Missouri, for the data of the initial right heart catheterization presented in case 1.

References

1. KISSIN, M.: Pulmonary insufficiency with a super-numerary cusp in the pulmonic valve. Am. Heart J. 12: 206, 1936.
2. KEZDI, P., PRIEST, W. S., AND SMITH, J. S.: Pulmonic regurgitation. Quart. Bull. Northwestern Univ. M. School 29: 368, 1955.
3. ABBOTT, M. E.: Atlas of Congenital Cardiac Disease. New York, American Heart Association, 1936.
4. OLESEN, K. H., AND FABRICUS, J.: Pulmonic valvular regurgitation during twenty-seven years after gonorrheal endocarditis. Am. Heart J. 52: 791, 1956.
5. EHRENHAFT, J. L.: Discussion of physiologic observations in experimental pulmonic insufficiency. J. Thoracic Surg. 30: 633, 1955.
6. FORD, A. B., HELLERSTEIN, H. K., WOOD, C., AND KELLEY, H. B.: Isolated congenital bicuspid pulmonary valve. Am. J. Med. 20: 474, 1956.
7. MORTON, R. F., AND STERN, T. N.: Isolated pulmonic valvular regurgitation. Circulation 14: 1069, 1956.
8. SEGEL, N., VAN LINGEN, B., RESNEKOV, V., AND MCGREGOR, M.: Isolated congenital pulmonary incompetence. South African M. J. 31: 1157, 1957.
9. DICKENS, J., RAVER, G. T., AND GOLDBERG, H.: Dynamic pulmonary regurgitation associated with a bicuspid valve. Ann. Int. Med. 48: 851, 1958.
10. LENDRUM, B. L., AND SHAFFER, A. B.: Isolated

congenital pulmonic valvular regurgitation. Am. Heart J. 57: 298, 1959.

11. SMITH, R. D., DUSHANE, J. W., AND EDWARDS, J. E.: Congenital insufficiency of the pulmonary valve, including a case of fetal cardiac failure. Circulation 20: 554, 1959.
12. FISH, R. G., TAKARA, T., AND CRYMES, T.: Prognostic considerations in primary isolated insufficiency of the pulmonic valve. New Eng. J. Med. 261: 739, 1959.
13. KJELLBERG, S., MANNHEIMER, E., RUDHE, V., AND JONSSON, B.: Diagnosis of Congenital Heart Disease. Chicago, The Year Book Publishers, Inc., 1959.
14. COLLINS, N. P., BRAUNWALD, E., AND MORROW, A. G.: Isolated congenital pulmonic valvular regurgitation. Am. J. Med. 28: 159, 1960.
15. BARGER, A. C., ROE, B. B., AND RICHARDSON, G. S.: Relation of valvular lesions and of exercise to auricular pressure, work tolerance and to development of chronic congestive failure in dogs. Am. J. Physiol. 169: 384, 1952.
16. FOWLER, N. O., AND DUCHESNE, E. R.: Effect of experimental pulmonary valvular insufficiency on the circulation. J. Thoracic Surg. 35: 643, 1958.
17. BLOUNT, S. G., JR., MCCORD, M. C., MUELLER, H., AND SWAN, H.: Isolated valvular pulmonic stenosis: Clinical and physiologic response to open valvuloplasty. Circulation 10: 161, 1954.

On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves

By DOMINIC JOHN CORRIGAN, M.D.

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That this visible pulsation of the arteries is owing to the mechanical cause here assigned is made evident by several circumstances. It is most distinct in the arteries of the head and neck, which empty themselves most easily into the aorta, and of course into the ventricle. In the arteries of the lower extremities, of even larger size than those which present it about the head and neck, it is not seen to any comparative degree, and most generally not at all while the patient is standing or sitting. It is much more marked in the arteries of the head and neck in the erect than in the horizontal posture; and a patient suffering under the disease himself, first pointed out a circumstance which is convincing of its being produced as asserted. He could increase the pulsation of the brachial and palmar arteries in a most striking degree by merely elevating his arms to a perpendicular position above his head. He thus enabled the brachial and palmar arteries to empty themselves more easily back upon the aorta. They became more flaccid, and then, on the next contraction of the ventricle, their diastole became comparatively greater, and their visible pulsation of course more marked. The same effect could be produced in the arteries of the lower extremities by lying down and elevating the legs on an inclined plane.

Origin of Both Great Vessels from the Right Ventricle

II. With Pulmonary Stenosis

By HENRY N. NEUFELD, M.D., JAMES W. DUSHANE, M.D., AND JESSE E. EDWARDS, M.D.

THE FIRST PAPER[1] of this series dealt with the origin of both great vessels from the right ventricle in the absence of pulmonary stenosis. It was indicated that the clinical picture in that condition might be confused with that of a large ventricular septal defect. Electrocardiographically, such an anomaly might be confused with either a persistent common atrioventricular canal[2] or the "AV commune" type of ventricular septal defect.[3]

The condition forming the basis for the present communication anatomically has in common with the foregoing anomaly the origin of both great vessels from the right ventricle, but pulmonary stenosis is also present. The hemodynamic, clinical, and electrocardiographic data resemble those in the tetralogy of Fallot.

This part of the study includes five cases in which both great vessels originated from the right ventricle associated with ventricular septal defect and pulmonic stenosis, and a sixth case, in which both great vessels took origin from the right ventricle and in which a common atrioventricular canal and pulmonic stenosis were associated.

The purpose of this paper is to summarize the clinical, hemodynamic, and anatomic findings in these cases. The differentiation of this anomaly from the tetralogy of Fallot with cyanosis is important because of the more complicated surgical approach in the former.

This anomaly has been described before in articles devoted to pathology, but only in recent years have a few cases been reported clinically.[1, 4-9]

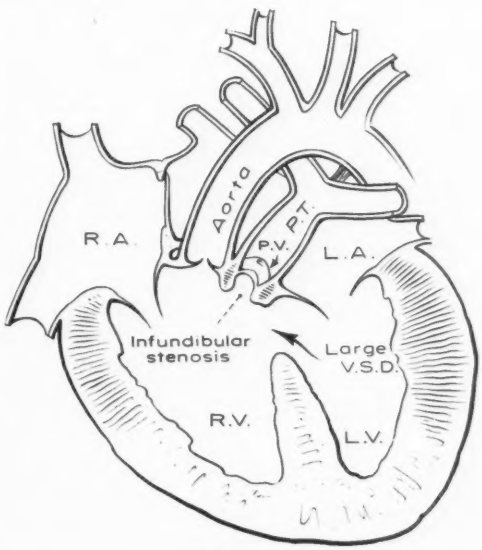

Figure 1

Diagrammatic representation of origin of both great vessels from right ventricle, with pulmonary stenosis and ventricular septal defect.

Witham,[10] in 1957, summarized reports of three cases from the literature and added two of his own, calling them "double outlet right ventricle, Fallot type."

Pathologico-anatomic Features

As in the cases in which both great vessels took origin from the right ventricle without pulmonary stenosis, the external view of the relationship of the great vessels in cases with pulmonary stenosis is very similar to the normal appearance, but important differences exist at lower levels within the heart (figs. 1-4).

The origin of the aorta lies to the right of the origin of the pulmonary artery, both

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Table 1

Clinical Data in Five Cases of Origin of Both Great Vessels from Right Ventricle, with Pulmonary Stenosis

			History			Physical findings							
Case	Age, yrs.	Sex	Cyanosis, age at onset	Shortness of breath	Palpitation	Cyanosis	Clubbing	Systolic thrill	Systolic murmur, grade and location*	Other murmurs	Second pulmonic sound	Blood pressure, mm. of Hg	Femoral pulses	Hemoglobin Gm./100 ml.
1	7/12	M	2 mos.	−	−	+	−	−	+	−			+	
2†	3	F	6 mos.	−	−	++	++	−	I (3)	−	Single, not diminished	115/75	+	19
3‡	13	M	2½ mos.	+	+	+	−	+	IV (4-5)	−	Single, not diminished	110/75	+	15.9
4†	8	M	8 mos.	+	+	+	+	+	III (3-4)	Machinery murmur; syst. ejection click	Accentuated	100/80	+	15.8
5	3½	M	Birth	+	+	+++	++	+	IV (3-4)	−	Diminished	100/75	+	18.2

*Roman numerals indicate grade of murmur; Arabic numbers in parentheses indicate those left intercostal spaces where the murmur was heard.

†Previous Blalock's procedure; a Potts operation also was done in case 4.

‡Previous Brock's procedure.

Figure 2

Origin of both great vessels from right ventricle, with infundibular stenosis, seen from right ventricular aspect. The ventricular septal defect (D.) lies caudal to the horizontal limb of the crista supraventricularis (C.S.). The vertical limb of the crista supraventricularis creates an infundibular chamber that is moderately stenotic and above which rises the pulmonary artery. P.V. = pulmonary valve. The aortic origin (A.V.) lies to the right of the pulmonary origin and at about the same body cross-sectional and coronal plane. The aortic valve lies above the horizontal limb of the crista supraventricularis, which separates the valves from the ventricular septal defect.

vessels being at about the same cross-sectional body plane. Internal views of the heart show that the aorta does not communicate with the left ventricle but arises completely from the right ventricle. The only outlet for the left ventricle is a ventricular septal defect.

The aortic valve lies above the horizontal limb of the crista supraventricularis, which separates the valve from the ventricular septal defect and from the atrioventricular valvular tissue. The aortic valve lies in the same coronal body plane as does the pulmonary valve.

Infundibular stenosis is created by a vertical limb of the crista supraventricularis.

One specimen (case 5) showed different features (fig. 5). The aorta originated from the right ventricle, lying to the right of the

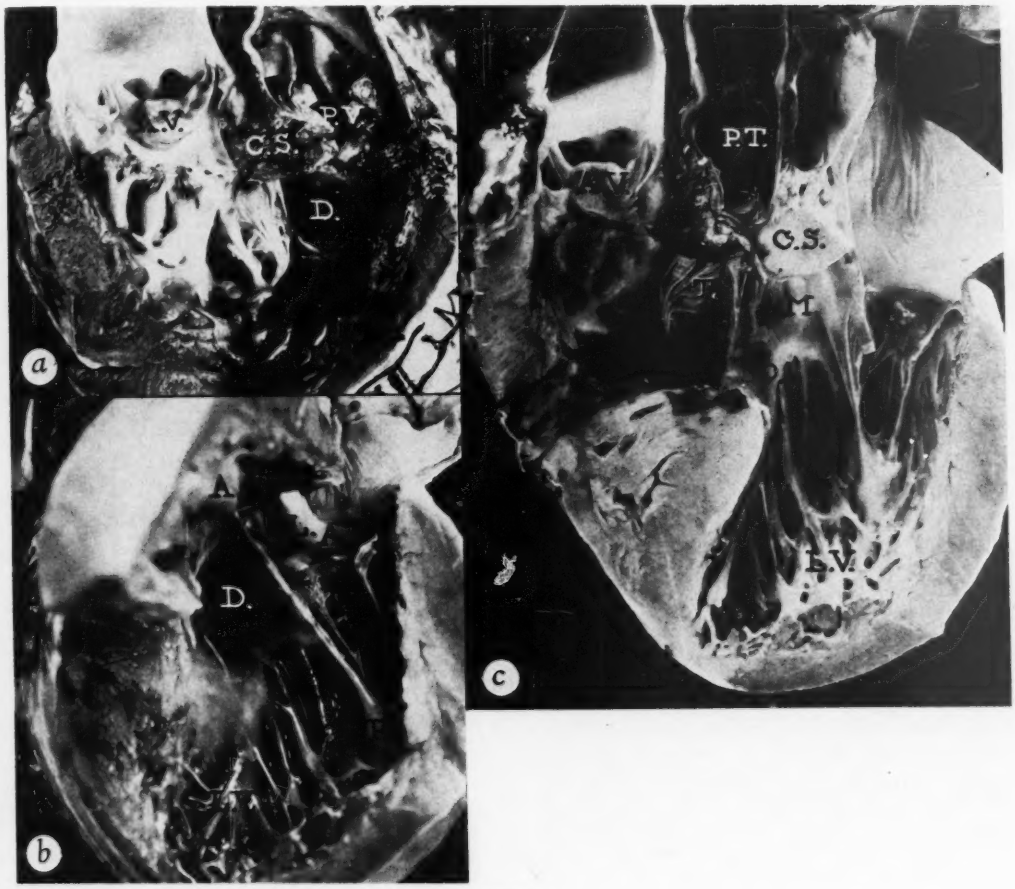

Figure 3

Origin of both great vessels from right ventricle, with infundibular stenosis. The specimen in this case resembles the one shown in figure 1. a. *Right ventricular aspect. A section has been made through the infundibular zone. The ventricular septal defect lies caudal to the crista supraventricularis (C. S.). A portion of the stenotic infundibular channel is present and lies below the pulmonary valve (P.V.). The aortic valve (A.V.) lies at the same cross-sectional body plane and to the right of the pulmonary valve, being separated from the atrioventricular valvular tissue by the horizontal limb of the crista ventricularis.* b. *Left atrium (L.A.) and left ventricle (L.V.). The anterior leaflet of the mitral valve has been stretched to prepare this illustration; it shows a normal caudal connection with the anterolateral papillary muscle (A.) and the posteromedial papillary muscle (P.). The ventricular septal defect (D.) lies ventral to the anterior leaflet of the mitral valve.* c. *Sagittal section through both ventricles and anterior leaflet of mitral valve. The posterior boundary of the ventricular septal defect (D.) is formed by the tissue of the septal leaflet of the tricuspid valve (T.) and the anterior leaflet of the mitral valve (M.), which joins the crista supraventricularis (C.S.). No continuity exists between the aortic valve and the atrioventricular valvular tissue. L.V. = left ventricle; P.T. = pulmonary trunk.*

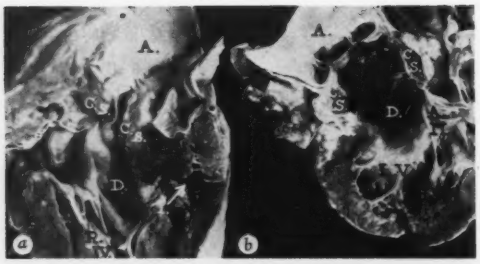

Figure 4

Origin of both great vessels from right ventricle, with infundibular stenosis. The ventricular septal defect is caudal to the crista supraventricularis. These illustrations show the relations of the aortic valve to the ventricular septal defect and the anterior leaflet of the mitral valve. They emphasize that, in the usual dissection, the fact that the aorta does not communicate with the left ventricle may be obscured by an illusion, which makes it appear to originate from the left ventricle when in fact it does not. a. *Right ventricular aspect. The aorta (A.) arises from the right ventricle. The aortic valve is separated from the ventricular septal defect (D.) by a horizontal limb of the crista supraventricularis (C.S.). A vertical limb of the crista supraventricularis creates an infundibular chamber(I.), which is stenotic. In this specimen, the incision has been carried from the left ventricle to the aorta, the crista supraventricularis being divided. The postmortem incision in the aorta has been sutured.* b. *Left ventricle and aortic valve. The specimen has been opened in the line of section shown in* a. *This figure shows apparent continuity between the aorta and the left ventricle, but this is an illusion because between the aorta, the left ventricle and the anterior leaflet of the mitral valve (A.M.) is a mass of muscle (C.S.), the crista supraventricularis, which lies above the ventricular septal defect (D.) and below the aortic valve. In normal hearts, a section through the left ventricle into the aorta in this perspective shows continuity between the aortic valve and the anterior leaflet of the mitral valve. In this heart, the crista supraventricularis separates these two valvular structures.*

origin of the pulmonary trunk. The posterior wall of the ventricular septal defect was formed by the septal leaflet of the tricuspid valve and the anterior mitral leaflet. Continuity was present between the mitral valvular tissue and the aortic valve, but the latter was positioned farther to the right than it is in the classic anatomic tetralogy of Fallot.

Table 2

Cardiac Catheterization Data in Case 2

Site	Pressure, mm. Hg	Oxygen saturation, per cent
Inferior vena cava	—	53
Superior vena cava	8/5	57
Right atrium	8/5	54-56
Right ventricular outflow	115/7	55
Main pulmonary artery	15/7	56
Right femoral artery	125/71	61

Clinical Findings

The clinical data in the first five cases are summarized in table 1. There were four boys and one girl; the youngest patient was 7 months of age and the oldest was 13 years. The first patient in this study was seen at the Mayo Clinic in 1936 (case 1 in table 1). All the patients had been cyanotic since the first months of life. Clubbing of the fingers was present in three instances. Three patients had a systolic thrill. The second sound at the pulmonary area was accentuated in one patient (case 4), on whom both a Blalock and a Potts operation had been done in the past. Squatting was not observed in any of the patients. None of the patients had experienced congestive cardiac failure or undue respiratory infections.

Electrocardiographic tracings were obtained in four of these five cases, and they were compatible with right ventricular hypertrophy of the type seen in the tetralogy of Fallot (fig. 6).

Roentgenograms were obtained in the same four cases (fig. 7). They revealed moderate enlargement of the heart and diminished pulmonary vasculature.

Hemodynamics*

Catheterization of the right side of the heart was performed in one instance (case 2). The data are shown in table 2. Severe desaturation of the peripheral arterial blood

*The authors gratefully acknowledge the assistance of Dr. E. H. Wood, who made available the hemodynamic data. Support for the latter was derived from grant no. H3532 of the National Heart Institute.

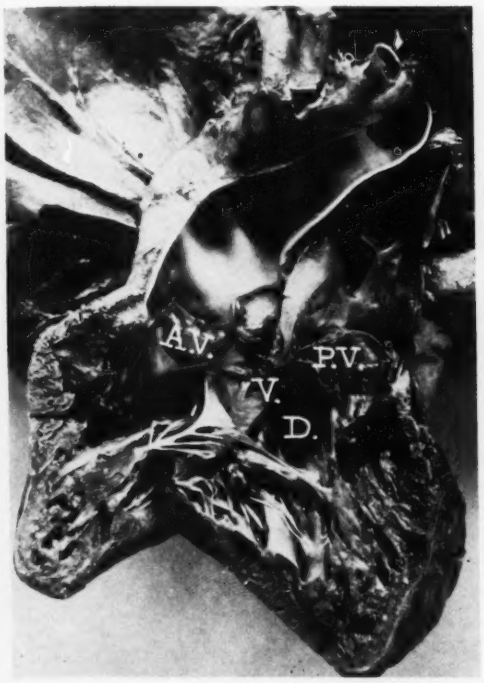

Figure 5

Case 5. A variant of the tetralogy of Fallot that in certain respects presents problems and anatomic relations more similar to those in origin of both great vessels from the right ventricle than to those in the classic tetralogy. The specimen shows the aortic origin (A.V.) from the right ventricle and to the right of the origin of the pulmonary trunk (P.T.). The left aspect of the aorta is at about the same plane as the ventricular septal defect (D.). The dorsal wall of the ventricular septal defect is formed by the septal leaflet of the tricuspid valve and the anterior mitral leaflet (V.). This specimen shows continuity between the mitral valvular tissue and the aortic valve, but the position of the aortic valve is considerably farther to the right than it is in the classic tetralogy of Fallot.

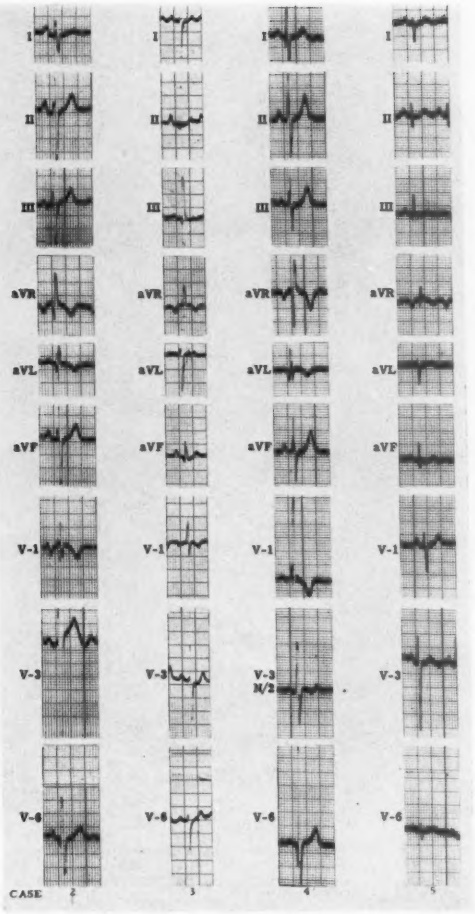

Figure 6

Electrocardiograms in cases 2 through 5.

was present. The oxygen saturation of right ventricular blood taken at the same time was 6 percentage points less than that of systemic arterial blood. The saturation of mixed venous blood ranged between 53 and 57 per cent. Pressures in the great veins and right atrium were normal. The right ventricular pressure was 115/7, expressed as millimeters of mercury. The catheter was manipulated to enter the pulmonary artery and was passed into the right lung field to the wedge position. The pressure in the right pulmonary artery was 10-15/0-5, and the wedge pressure was 2-4 mm. No significant difference was noted between the oxygen saturation in the main pulmonary artery and that in the outflow portion of the right ventricle. When the catheter was withdrawn across the pulmonary valve, the region of obstruction appeared to be sharply localized to a region at or near the pulmonary valve, since a high systolic ventricular pressure was recorded immediately upstream to the pulmonary valve. Further changes in pressure were not

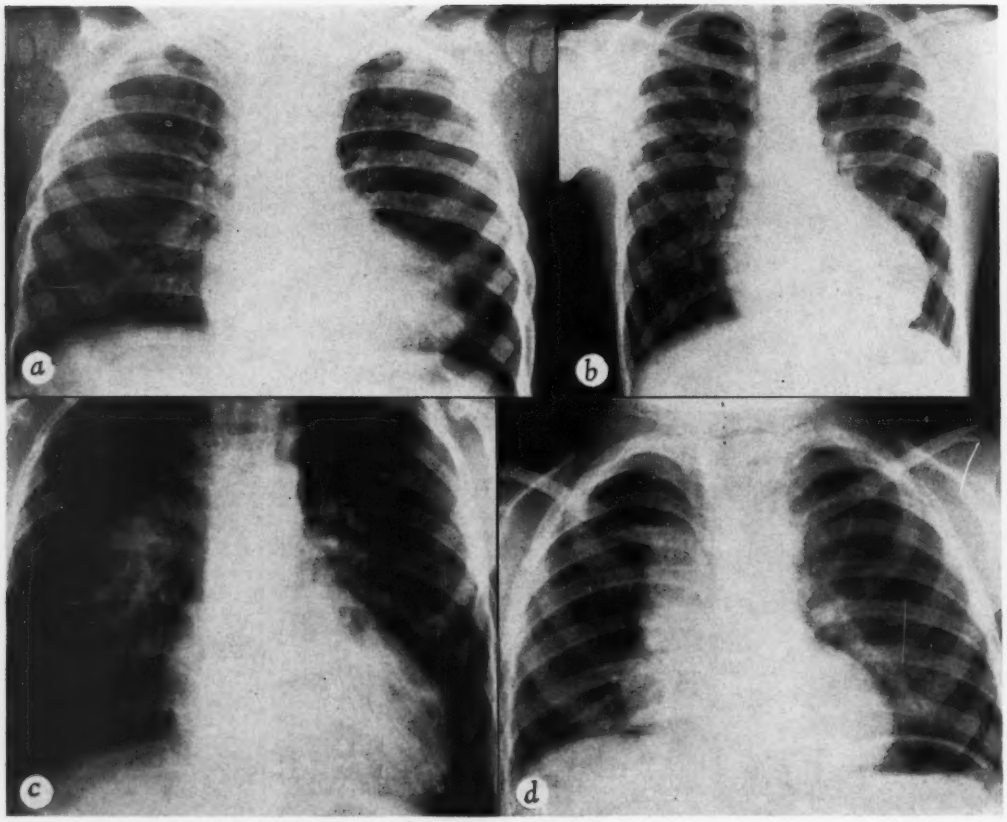

Figure 7

a-d. *Thoracic roentgenograms in cases 2 through 5.*

Table 3

Cardiac Catheterization Data in Case 6

Site	Pressure, mm. Hg	Oxygen saturation, per cent
Superior vena cava	—	53
Right atrium	8/3	57
Left atrium	11/7	79-85
Right ventricle	116/4	65-67
Femoral artery	121/63	72
Pulmonary vein	10/5	99

observed when the catheter was withdrawn from this position to the lower part of the right ventricle.

The catheter was then advanced, and it entered the aorta. The aortic arch was located on the left.

Indicator-dilution curves were recorded at the right radial artery after injections of cardio-green dye into the main pulmonary artery, the lower part of the right ventricle, the aorta and the superior vena cava. The contours of the curves obtained after injection into the superior vena cava, right ventricle, and aorta were similar or almost identical. The similarity of the contours of curves recorded after injections into the superior vena cava and right ventricle excluded the possibility of preferential injection into the aorta from the right ventricle. The close similarity of the curves indicated an extremely large right-to-left shunt and practically an absence of flow from the right ventricle directly to the pulmonary artery.[10]

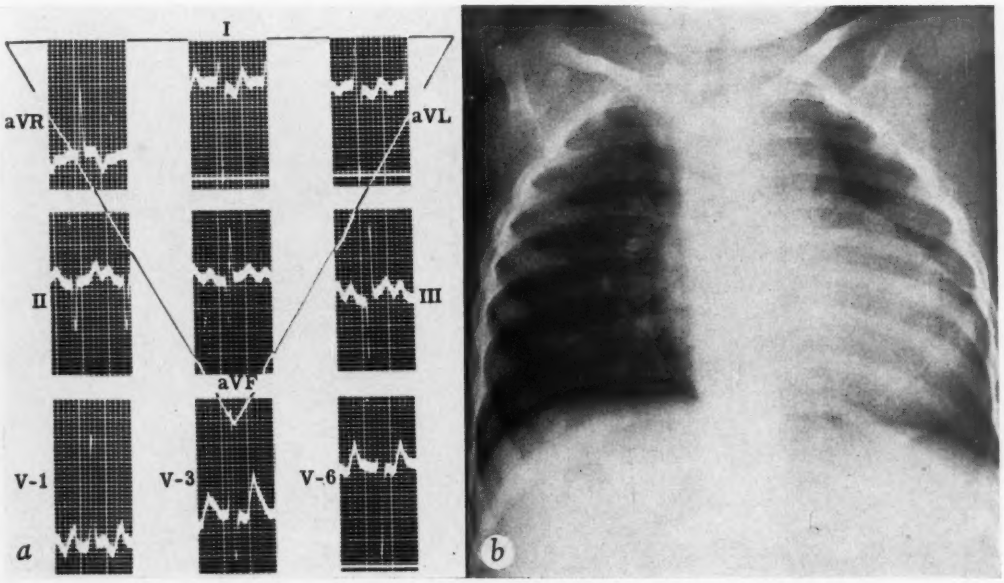

Figure 8

Case 6. a. *Electrocardiogram of a 3-year-old girl who had persistent common atrioventricular canal.* b. *Thoracic roentgenogram in same case.*

The hemodynamic state in this anomaly is similar to that present in severe tetralogy of Fallot with cyanosis. The pressures in both ventricles are equal, and a pressure gradient exists between the right ventricle and the pulmonary artery. Peripheral oxygen desaturation is present in all cases.

In some instances, relatively complete mixing of systemic venous and left ventricular blood in the right ventricle might be expected to occur; when this is present, closely similar values for oxygen saturation in the systemic and pulmonary arteries would be found. On the other hand, some of the patients will show poor mixing in the right ventricle. In such instances, a streaming effect apparently exists, the left ventricular blood being shunted preferentially through the ventricular septal defect directly into the aorta, and the right ventricular blood being directed into the pulmonary artery. In these cases, the oxygen saturation of the pulmonary arterial blood will be significantly less than that of the systemic arterial blood. This situation prevailed in case 2 (table 2).

Diagnostic Clues

A clue to the correct diagnosis of the origin of both great vessels from the right ventricle with pulmonary stenosis can be obtained during cardiac catheterization or angiocardiography or both. Utilizing a two-catheter technic (venous and aortic) and bearing in mind the anatomic relationship of the semilunar valves, one might prove that both semilunar valves are in the same cross-sectional and coronal body planes. The same applies to biplanar selective angiocardiography. Another clue that can be obtained in angiocardiography is the relationship of the ventricular septal defect to the crista supraventricularis. In the tetralogy of Fallot, the crista supraventricularis is ventral to the ventricular septal defect; in origin of both great vessels from the right ventricle with pulmonary stenosis, the crista supraventricularis is cephalad to the ventricular septal defect.

Report of Unusual Case

The afore-mentioned sixth case showed additional interesting pathologic features.

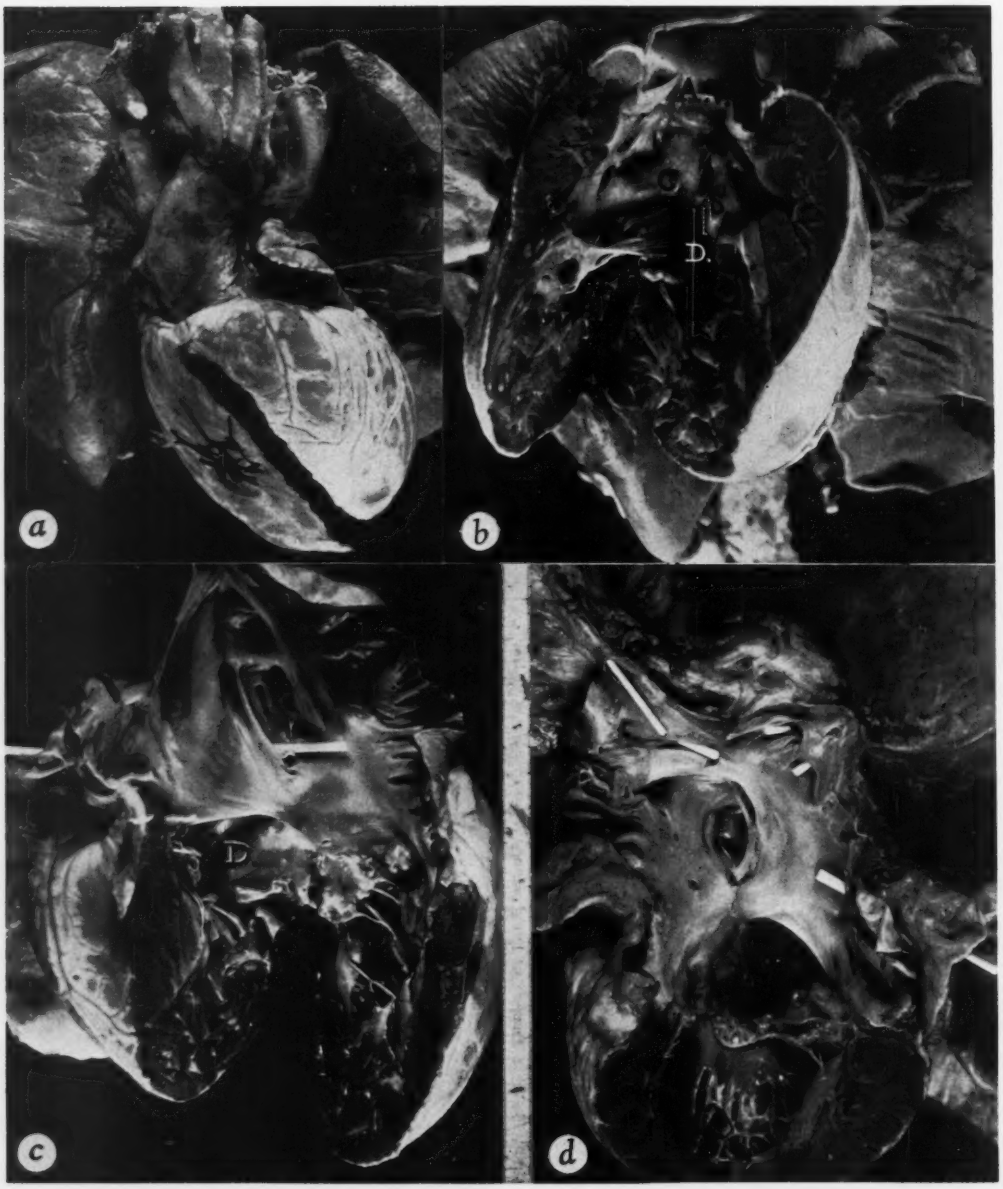

Figure 9

Case 6. Origin of both great vessels from right ventricle, with persistent common atrioventricular canal. In this unusual heart, the relative positions of the aorta and the pulmonary trunk are contrary to those in the usual examples of origin of both great vessels from the right ventricle. In the latter condition, the aortic origin lies to the right of the pulmonary trunk; in this specimen, the aortic origin lies ventral to the pulmonary trunk. a. *External view of heart and great vessels, showing prominent ventral position of aorta.* b. *Interior of right ventricle. The aorta (A.V.) arises from the right ventricle above the crista supraventricularis (C.S.), which creates an infundi-*

Case 6. A 3-year-old girl was brought to the clinic in June 1958, for evaluation of a cardiac lesion and the possibilities of surgical intervention. The child had been cyanotic since birth, and her physical and mental development was impaired.

Cyanosis and clubbing were present. The heart was quiet, and a harsh systolic murmur (grade 2) was best heard at the second and third left intercostal spaces. The second cardiac sound in the pulmonic area was single and diminished. The femoral pulsations were normal.

The electrocardiogram showed a normal sinus rhythm. The mean manifest QRS electric axis was —170 degrees, with a figure-of-eight loop in the frontal plane, the initial portion of the loop being counterclockwise. Signs of right ventricular hypertrophy were present in the thoracic leads (fig. 8*a*).

Roentgenologic examination revealed cardiac enlargement and decreased pulmonary vasculature (fig. 8*b*).

Cardiac catheterization was performed (table 3). The pulmonary artery was not entered. The left atrium was entered in a retrograde fashion from the ventricle, suggesting either an anatomically common ventricle or a persistent common atrioventricular canal type of defect. The pulmonary venous saturation was greater than the left atrial saturation, indicating a right-to-left shunt at the atrial level. The most likely diagnosis considered from the catheterization data was a common ventricle or a persistent common atrioventricular canal associated with pulmonic stenosis.

An infundibular resection was performed at operation. The patient died on the same day.

Pathologic Findings. Necropsy revealed that the great vessels were transposed; both vessels originated from the right ventricle, but the pulmonary trunk lay dorsal to and to the right of the ascending aorta (fig. 9). The ascending aorta was considerably wider than normal, while the pulmonary trunk was thin-walled and narrow, measuring only about 8 mm. in diameter.

Significant venous anomalies were present. Bilateral superior venae cavae were present; the bridge between the two that is present under normal conditions also existed in this case. The right superior vena cava entered the right atrium in the normal position, while the left superior vena cava entered the left atrium at a position comparable to that at which the right one entered the right atrium. Two inferior venae cavae were present that perforated the diaphragm on either side of the esophagus. The right one measured about 1.5 cm. in diameter, while the left measured 1 cm. The right inferior vena cava entered the right atrium in a normal position, while the left inferior vena cava entered the left atrium in the posteroinferior aspect, inferior to the left inferior pulmonary vein. The pulmonary veins entered the left atrium normally.

The interior of the heart showed an atrial septal defect measuring about 1 by 0.5 cm. involving the fossa ovalis. No lower limbus of the fossa ovalis could be identified. The lowermost portion of the atrial septum contained a large defect characteristic of that associated with a persistent common atrioventricular canal. A common atrioventricular valve served both sides of the heart. The lowermost part of the defect in this region was formed by the crest of the underlying ventricular septum. Thus, the defect presented a picture of the complete variety of persistent common atrioventricular canal. Beneath the posterior leaflet were many interchordal spaces that allowed interventricular communication. A small number of interchordal spaces were found beneath the anterior leaflet of the common atrioventricular valve. The coronary sinus was absent. Two ventricles were present, each being about the same size, although the right ventricular muscle appeared somewhat thicker than the left. The left ventricle did not have any vessel of egress. This chamber communicated with the right side by way of the subvalvular communications in relation to the persistent common atrioventricular canal that already has been described; in addition, a defect about 8 mm. in diameter was present in the muscular part of the most superior anterior portion of the ventricular septum.

bular chamber that leads to the origin of the transposed pulmonary artery. The ventricular septal defect (D.) lies caudal to the crista supraventricularis. c. *Right side of the heart, showing a typical example of the complex nature of persistent common atrioventricular canal. The lower part of the atrial septum contains a defect (D.), the lower border of which is formed by atrioventricular valvular tissue. The latter is represented by a valve common to both sides of the heart, representing the complete variety of persistent common atrioventricular canal. In this case, the inferior vena cava entered the left atrium. The probe shows an additional atrioseptal defect at the fossa ovalis.* d. *Left side of heart, showing the typical deformities of persistent common atrioventricular canal. The upper probes are in normally situated pulmonary venous connections with the left atrium. A probe in the right lower part of the photograph shows the entrance of the inferior vena cava into the left atrium.*

The aorta arose entirely from the right ventricle. Posterior to the origin of the aorta was a narrow muscle-walled tract measuring only about 3 mm. in diameter that led to the pulmonary artery beyond. Evidence of recent surgical intervention in relationship to the subpulmonary stenosis was present. The aortic arch was on the left side. The ductus arteriosus was closed. The bronchial arteries appeared to be enlarged.

The pathologic diagnoses included origin of both great vessels from the right ventricle, with pulmonary stenosis; persistent atrioventricular canal (complete variety); anomalous connection of a persistent left superior vena cava with the left atrium; bilateral inferior venae cavae, the left one communicating with the left atrium; absence of the coronary sinus.

Comment. Despite the pathologico-anatomic findings of significant pulmonary stenosis, the initial vectors in the electrocardiogram in the frontal plane were directed to the left, as they are in persistent common atrioventricular canal, which was present in this patient.

Summary and Conclusions

Clinical, hemodynamic, and pathologico-anatomic findings were studied in six cases in which both great vessels took origin from the right ventricle in the presence of pulmonary stenosis. This condition is indistinguishable from the tetralogy of Fallot, with cyanosis on the basis of clinical, electrocardiographic, and radiologic findings. The hemodynamics are also similar in both conditions.

The more complicated surgical approach in the condition under consideration emphasizes the importance of its differentiation from the usual case of tetralogy of Fallot with cyanosis.

Only angiocardiography and cardiac catheterization might be of diagnostic help, if one bears in mind the anatomic characteristics of this condition. The fact that both the aortic and pulmonary valves are at the same horizontal body level in this anomaly must be considered at angiocardiography. Also, the fact that the crista supraventricularis is cranial and more dorsal to the ventricular septal defect may be of some diagnostic help at angiocardiography. Careful analysis of the exact position of the semilunar valves during combined catheterization of the right side of the heart and the aorta is of some diagnostic importance.

References

1. NEUFELD, H. N., DuSHANE, J. W., WOOD, E. H., KIRKLIN, J. W., AND EDWARDS, J. E.: Origin of both great vessels from the right ventricle. I. Without pulmonary stenosis. Circulation 23: 399, 1961.
2. TOSCANO-BARBOSA, E., BRANDENBURG, R. O., AND BURCHELL, H. B.: Electrocardiographic studies of cases with intracardiac malformations of the atrioventricular canal. Proc. Staff. Meet., Mayo Clin. 31: 513, 1956.
3. NEUFELD, H. N., TITUS, J. L., DuSHANE, J. W., BURCHELL, H. B., AND EDWARDS, J. E.: Isolated ventricular septal defect of the persistent common atrioventricular canal type. Unpublished data.
4. SPITZER, A.: The Architecture of Normal and Malformed Hearts: A Phylogenetic Theory of Their Development. Springfield, Illinois, Charles C Thomas, 1951, 145 pp.
5. PEACOCK, T. B.: Malformations of the Human Heart. Ed. 2, London, J. Churchill & Sons, 1866, 204 pp.
6. ABBOTT, M. E. S.: Atlas of Congenital Cardiac Disease. New York, American Heart Association, 1936, 62 pp.
7. EDWARDS, J. E.: Congenital Malformations of the Heart and Great Vessels. *In* Gould, S. E.: Pathology of the Heart. Ed. 2, Springfield, Illinois, Charles C Thomas, 1960, pp. 260-496.
8. LEV, M.: Autopsy Diagnosis of Congenitally Malformed Hearts. Springfield, Illinois, Charles C Thomas, 1953, 194 pp.
9. BRAUN, K., DE VRIES, A., FEINGOLD, D. S., EHRENFELD, N. E., FELDMAN, J., AND SCHORR, S.: Complete dextroposition of the aorta, pulmonary stenosis, interventricular septal defect, and patent foramen ovale. Am. Heart J. 43: 773, 1952.
10. WITHAM, A. C.: Double outlet right ventricle: A partial transposition complex. Am. Heart J. 53: 928, 1957.

CLINICAL PROGRESS

Cardiac Amyloidosis

By ROBERT S. ELIOT, M.D., HUGH J. MCGEE, M.D., AND S. GILBERT BLOUNT, JR., M.D.

AMYLOIDOSIS was first described by Wilks in "The Guys Hospital Report" of 1856.[1] It was referred to at that time as "lardaceous disease," obviously because of the physical similarity of amyloid to lard. Very few cases were reported until 1908 when Beneke and Bönning[2] reported their experience. In 1929 Lubarsch[3] reported three cases and suggested the criteria for diagnosis, but by 1930 only 10 cases were in the literature.[1-7]

Very little appeared in the English or American writings until the mid 1930's. By 1950 Higgins and Higgins[8] had collected 71 cases from the literature and added their own experience. Since their report, many other cases have been added and the concept of its rarity has faded in the light of these recent reports. The question of etiology remains to be answered, as well as the problem of terminology and classification. The lack of clarity in both these areas is demonstrated by the following terminology:[9-23] atypical amyloidosis, paramyloidosis, unusual amyloid deposits, idiopathic amyloid disease, primary amyloidosis, and tumor-forming amyloid. This problem in terminology has made it difficult to review with accuracy the literature on this subject.

Perhaps the most workable classification is that suggested by Reimann, Koucky and Eklund:[22] (1) primary amyloidosis—in which no concomitant disease or explanation is found; (2) secondary amyloidosis—which occurs in conjunction with chronic suppurative, malignant, or other wasting diseases; (3) localized tumor-forming amyloidosis; (4) amyloidosis associated with multiple myeloma. To date this classification has not been uniformly accepted.

So-called primary amyloidosis more commonly involves the heart than any other organ.[23] Its presence is rarely suspected ante mortem and thus it represents a problem in cardiac diagnosis that has not as yet been thoroughly elucidated.

Mulligan recently reported 17 cases of cardiac amyloidosis and reviewed the literature.[24] Subsequently, an unusual patient with this condition came to our attention and brought to mind the problem of diagnosis from a clinical and laboratory standpoint. None of our patients was diagnosed ante mortem.

The purpose of this paper is to present 20 cases of cardiac amyloidosis (19 from the University of Colorado Medical Center and one from the Denver VA Hospital); to report an unusual case; to review 82 additional cases from the literature;[25-73] and to emphasize certain electrocardiographic findings.[26-40] It is the hope that emphasis on certain findings will aid in predicting the type of patient in whom cardiac amyloidosis is to be suspected, so that more cases may be studied ante mortem.

First a patient is presented who is believed to have the largest amyloid heart ever reported.

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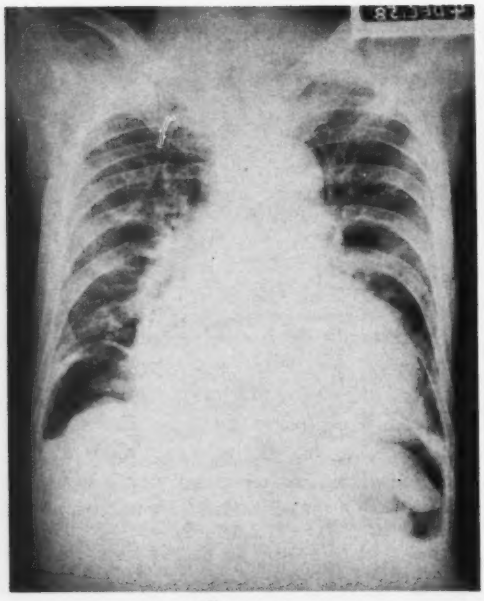

Figure 1

X-ray reveals air under the diaphragm, gross cardiomegaly, and prominent vascular markings.

Case Report

A.B. was a 76-year-old Negro man who was admitted to the Denver VA Hospital with complaints of abdominal and chest pain for 3 days and dyspnea, ankle edema, and progressive weakness of 6 months duration. The past history revealed digitalis and diuretic treatment for 3 years, but elaboration on this and other historical data was impaired by his near terminal state.

Physical examination revealed an emaciated elderly, ill Negro with a blood pressure of 80/20 and an irregular heart rate of 80 per minute. The neck veins were distended beyond the angle of the jaw, the heart was enlarged beyond the midaxillary line, and basilar rales and 2 to 3 plus pitting edema were present. The abdomen was rigid and tender, with maximal point tenderness to the left of the umbilicus. Rectal examination revealed a guaiac-positive stool.

The admission white blood cell count was 3,800; the hemoglobin was 16 Gm. per cent; the serum glutamic oxaloacetic acid transaminase was 72 units. Serum electrolytes were within normal limits. Chest roentgenogram revealed a grossly enlarged heart and free air under the diaphragm (fig. 1). The electrocardiogram is shown in figure 2.

At surgery a 3-mm. perforation in an anterior gastric ulcer was closed and 1,500 ml. of cloudy yellow fluid were removed. Following the procedure, the patient failed to breathe well, ventricular fibrillation developed, and death ensued, despite procaine amide and precordial pounding, which temporarily restored normal sinus rhythm.

The body was poorly nourished, was 62 inches long, and weighed 90 pounds. The heart weighed 1,090 Gm. and occupied nearly half of the thoracic space. This heart weight is particularly remarkable in relation to the total body weight of 41 Kg. in that it represented 2.7 per cent of body weight or more than five times normal. Anteriorly the epicardium was mottled dark red and elsewhere slightly roughened and marked by opaque gray plaques ranging from 1 to 10 mm. in diameter. The myocardium was firm and rubbery, and the chambers failed to collapse when emptied of blood. The cut surfaces of the myocardium were pale yellow-brown and gray mottled, waxy, and semitranslucent. In the anterior portions of the right and left ventricles and interventricular septum, dark red blood dissected among muscle bundles and separated them. The endocardium of the atria was thickened, yellow-tan, and marked by myriads of yellow-gray nodules, which projected slightly above the surface and averaged less than 0.5 mm. in diameter. The nodules did not extend onto the atrial surfaces of the valves, which were intact except for slight fibrous thickening at their free margins. The chordae tendineae were slightly thickened. The endocardium of the ventricles was focally thickened, opaque and gray-white to pale yellow-tan, and showed no nodules (figs. 3 and 4). The coronary arteries were patent and generally normal, except for slightly elevated yellow intimal plaques that moderately narrowed the lumen. The remainder of the gross examination was essentially negative, except for a recently closed, 1.5-cm. gastric peptic ulcer and a diffuse purulent peritonitis.

Microscopically, masses of amyloid had infiltrated diffusely among the muscle fibers and capillaries of all chambers. Amyloid was present in the media and intima of all arteries and veins, sometimes forming masses that bulged into the lumen (fig. 5). In the endocardium of the atria, masses of amyloid were present just beneath the endothelium and elevated it. Deposits were less prominent and more diffuse in the endocardium of the ventricles. Amyloid focally encased fat cells in the epicardium or was deposited in large plaques. In the myocardium most of the amyloid was diffusely deposited in the interstitial tissue among the muscle fibers (fig. 5). Often it formed definite rings about fibers. In most severely involved areas, muscle fibers were decreased in size and some had disappeared. In other areas the muscle fibers were considerably enlarged and had swollen irreg-

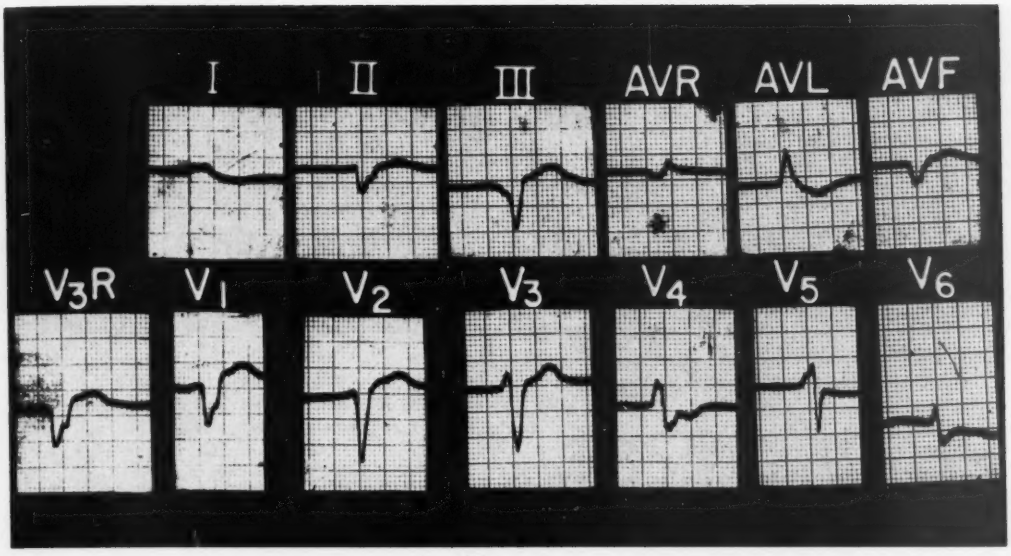

Figure 2

An electrocardiogram reveals left axis deviation with prolongation of the QRS (0.14 second), uniformly flat or inverted T waves, QS in II, III, and aV_F. The major T vector is 180° from the major QRS vector. Without previous tracings, the diagnosis is obscure. Left bundle-branch block and parietal block are possibilities. No P waves are seen in any lead, and atrial fibrillation was believed to be present.

ular hyperchromatic nuclei. In the anterior wall of the left ventricle there was massive extravasation of blood among the fibers (fig. 6). Sections to demonstrate the conduction system were made, but diffuse infiltration of amyloid obliterated the fibers of the system. The amyloid stained purplish-violet with crystal violet. A combination of the crystal violet and reticulum stains showed an intimate association of amyloid and reticulum. The amyloid appeared to coat the reticulum fibers, which were often irregularly thickened and fractured (fig. 7). Amyloid was fairly abundant in alveolar septa and blood vessels of the lungs, and sparse in the muscularis of the stomach and intestine, stroma of the prostate gland, blood vessels of the adrenal glands, pancreatic islets, and stroma of the kidney.

Comment

This patient illustrates many common interesting facets of the disease that deserve emphasis:

1. Age—eighth decade.
2. Sex—male.
3. Presentation with gastrointestinal symptoms.
4. Three-year history of progressive congestive failure refractory to the usual forms of therapy.
5. Poor nutritional state.
6. Left axis deviation, ventricular conduction disturbance, and low voltage QRS, ventricular premature contractions, and, finally, ventricular fibrillation.
7. A very enlarged heart without good explanation: The weight of 1,090 Gm. is larger than the largest amyloid heart found in the literature, particularly in relation to the patient's weight of 41 Kg. The heart weight was 2.7 per cent of total body weight, or five times normal.
8. Maximum involvement of the heart rather than other organs.
9. Minimal evidence of coronary atherosclerosis.
10. No evidence of coexisting chronic illness.

Discussion

Age Distribution

Sixteen of our 20 patients were between 80 and 90 years of age. Three were in their 70's and one was 90 plus. The range in the literature is from 20 to 101 years. More than 50 per cent are 70 years or older.

Sex Distribution

The male-to-female ratio, by virtue of the number of males autopsied, is 2.5 times

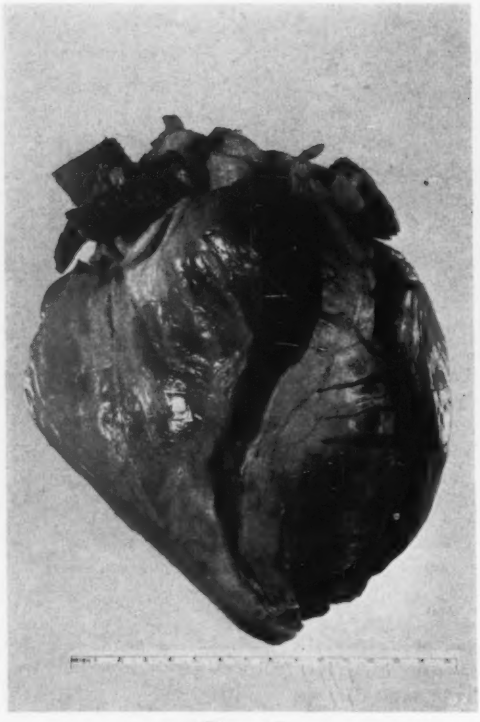

Figure 3

The heart, showing its gross size and hemorrhage in the anterior wall of the left ventricle.

greater than the number of females at this institution. This may vary in other institutions as well. Josselson[31, 32] reported a sex ratio of 1.64 in 44 cases and Husselmann,[65] 1.75 in 40 cases. No conclusions are drawn from our study, since selection is involved.

Race

Amyloidosis has been reported in both white and Negro races. One patient in our series was Negro. Jones and Frazier[38] reported 14 Negro cases of cardiac amyloidosis. Picking up one case from Ohliger[42] and another from Golden,[66] we know of at least 17 cases of 102 in the Negro. We are unaware of reports of this disease in the oriental races.

Incidence of Amyloidosis as a Primary Cause of Death

Amyloidosis was the primary cause of death in 11 of our 20 cases. In these instances, congestive failure was uniformly the cause

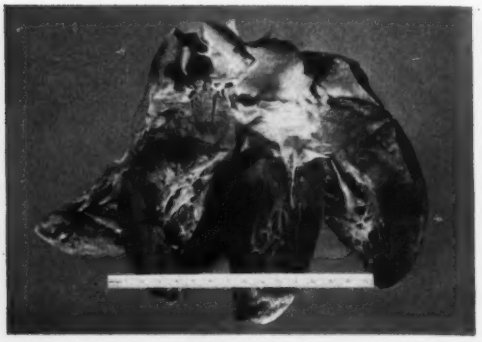

Figure 4

Incisions through the anterior wall of the left ventricle demonstrate the extensive infiltration of amyloid and the prominent hypertrophy.

of death, with a probable effect in two cases from ventricular arrhythmias. Amyloidosis played a secondary role in the remaining nine cases.

Incidence of Congestive Failure

Nine of our patients presented with refractory congestive failure; 19 of the 20 had definite findings of congestive failure at one time or another. Left ventricular failure was present first in all but three cases. Once heart failure developed, death ensued within 6 months to 2 years. It is significant that the failure was uniformly persistent and progressive, despite all therapeutic measures. The incidence of these symptoms and findings in our cases was higher than in the cases reviewed by Higgins and Higgins.[32]

Incidence of Gastrointestinal Complaints

Three of our patients (15 per cent) presented with perforated peptic ulcer; six others had various gastrointestinal complaints such as dyspepsia and postprandial distress making a total of nine patients, or 45 per cent.

Incidence of Cardiac Murmur

Twelve of our patients (60 per cent) were reported to have systolic murmurs (usually grade I or II) located at the left sternal border or apex. Insufficient data were available to define these murmurs further. No diastolic murmurs were recorded. In the literature we found murmurs recorded in-

Table 1

Electrocardiographic Findings in Fifteen Cases Reported in the Literature and Sixteen Cases from our Experience

Electrocardiographic findings	Summary of literature	Our experience	Per cent or average
Low voltage	11	14	80%
Normal axis	3	4	22.5%
(a) Average heart weight	301 Gm.	283 Gm.	290 Gm.
Left axis deviation and parietal block	7	9	52.0%
Borderline left axis deviation	0	2	6.4%
Left axis deviation and peri-infarction block	1	0	3.2%
Total with left axis deviation	8	11	61.6%
(a) Average heart weight	588 Gm.	415 Gm.	463.4Gm.
(b) Number of infarcts	1	1	6.4%
Right axis deviation	4	1	16.0%
(a) Average heart weight	486.6 Gm.	400 Gm.	469.2 Gm.
First degree A-V block	7	4	34.3%
Right bundle-branch block	1	1	6.4%
Left bundle-branch block	1	2	9.6%
Atrial fibrillation	5	4	29.0%
Ventricular premature contractions	6	4	32.0%
T-wave abnormalities	6	4	32.0%
Definite myocardial infarction	1	1	6.4%
Inverted QRS V_1-V_3 (after Bernreiter[9])	8	8	52.0%

*Heart weights do not include the 1,090-Gm. heart

frequently and they were systolic and poorly defined. No significant valvular lesions were associated with the murmurs in our patients. The finding of a nonspecific systolic murmur in the aged patient without clinical or pathologic evidence of disease is common in our experience. Therefore, we attach no value to systolic murmurs in making the diagnosis of this disease.

Incidence of Coronary Atherosclerosis

Atherosclerotic involvement of the coronary arteries was graded as minimal, moderate, or severe with infarction. Only four patients had associated severe coronary atherosclerosis. Three had moderate atherosclerosis, but the remainder were minimally involved. Six patients recorded in the literature but none of our series had angina.

Incidence of Hypertension

One of our patients had a diastolic blood pressure greater than 110 mm. Hg. Only four patients with a diastolic pressure greater than 110 mm. Hg were found in 82 cases in the literature.

Average Heart Weight

The heart weight was noted in 76 of the 82 cases reviewed in the literature. In these patients the average weight was 472 Gm., and almost all had clinical cardiac disease. In our series (not including the 1,090-Gm. heart) the average was 414 Gm.; including the above case, our average would be 442 Gm., but it is considered that the latter is not a representative figure (table 1). In general, hearts that were minimally involved (microscopic evidence only) had normal weights and no abnormality of the axis. Hearts that were grossly involved were heavier and demonstrated left or right axis deviation in a high percentage.

Electrocardiographic Findings

For this study, only those patients from the literature[23-73] were analyzed in which photographs of electrocardiograms were in-

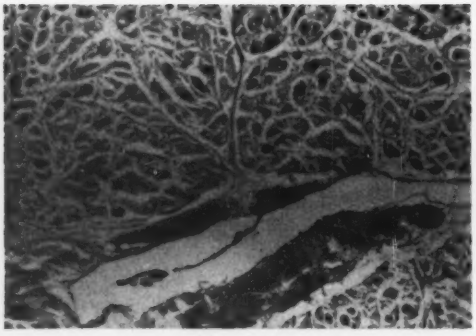

Figure 5

Large deposits of amyloid are present beneath the intima of the coronary sinus. A few hypertrophied muscle fibers are present among the amyloid which diffusely infiltrates around the muscle fibers. Hematoxylin and eosin stain.

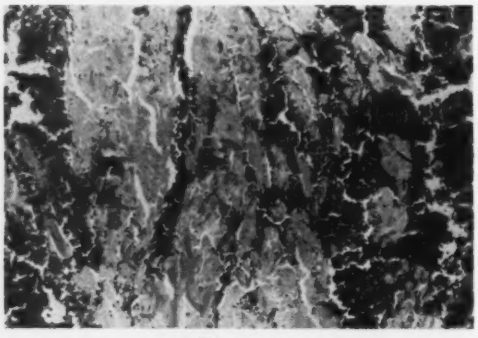

Figure 6

A section through the contusion in the anterior wall of the left ventricle.

cluded as well as heart weight, degree of coronary atherosclerosis, and other essential clinical data (table 1).

The finding of left axis deviation with parietal block in a significant number of patients might be expected in view of the mechanism of left axis deviation. If the superior branch of the left bundle were permeated with foreign hyaline material, the usual conductive pathways might well be impaired, causing the electromotive force to take a more circuitous route with resultant left axis deviation.[74] The differentiation between this condition and left bundle-branch block requires previous tracings, which are not always available.

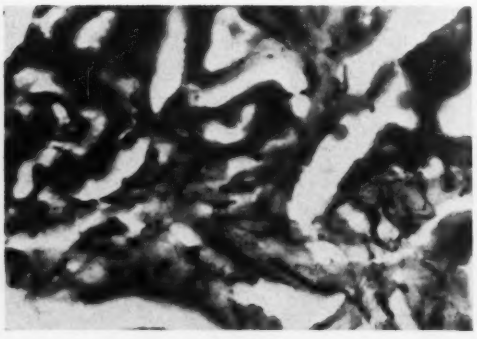

Figure 7

The amyloid appears to be deposited as a coating upon the fractured, irregularly swollen reticulum fibers. Crystal violet and Wilder reticulum stain.

Right axis deviation was observed in four cases in the literature and in one of our cases. Because these cases lacked an R′ in V_{3R} or V_1, the true $S_1S_2S_3$ syndrome could not be established. The right axis deviation in our single case was unexplained. No definite conclusions could be drawn from the other four cases, except that the right axis deviation was more frequently associated with amyloid hearts weighing more than 450 Gm.

Two of our cases showed sufficient coronary atherosclerosis to suggest it as the cause for the axis deviation. Hearts with right or left axis deviation were, however, much heavier than those with normal axis. This observation emphasizes the importance of finding gross cardiomegaly before suggesting amyloidosis to account for clinical heart disease.

The uniformly low voltage QRS has been commented upon by many authors as well as P-R prolongation and frequent premature ventricular contractions. Atrial fibrillation in the absence of significant coronary atherosclerosis was present in almost 30 per cent of cases. It is probable that our patient with the 1,090-Gm. heart had atrial fibrillation, but this was not definitely established by the technically poor record.

Etiology

Neither the etiology nor the exact chemistry

of amyloid is as yet understood. The theory that chondroitin-sulfuric acid is at least a building block in amyloid has not been substantiated.[75, 78]

Block[79] recently reported the presence of an atypical serum protein component of five patients with familial primary systemic amyloidosis. It appears to be located between the alpha and beta globulins and he calls it an A_2' globulin. This has apparently not been demonstrated in acquired cases as yet. Schneckloth and Page[80] have recently reported a case with elevation of B_1 lipoproteins as well as the A_2 fractions, in a patient with nephrotic syndrome secondary to amyloidosis.

Mulligan[24] has pointed out that "the apparent common denominators of amyloidosis of the heart are senility and malnutrition." Fifteen of our cases had impaired food intake due to gastrointestinal lesions (seven cases), cancer (three cases), and other causes (five cases). The low weight of the liver in these cases lends additional support to the thesis of malnutrition. He objected to the term "primary," indicating that in view of the associated findings this disease is probably always secondary, if only the cause were known. Whether it is reduced capacity for the synthesis of serum proteins[81] or the synthesis of abnormal proteins,[20] hypoalbuminemia,[33, 37, 80, 82] thiamine deficiency,[74, 83-86] or some other unrecognized metabolic abnormality, remains to be clarified.

In 1948 King[78] correlated the incidence of amyloid with age and proposed that amyloid disease was more common than had been suspected. Edwards[87, 88] found amyloid in five of 100 consecutive autopsies of men in the ninth decade. Certainly, most patients are past 70 years of age.

Distribution in the Heart

Edwards[88] reported that all cases of cardiac amyloidosis demonstrated gross lesions of the endocardium, of the right atrium, and often of the left atrium, and that these lesions were tiny translucent gray-to-pink elevations from pinpoint in size to 5 mm. in diameter. According to Dahlin and Edwards,[68, 87, 88] the atrial endocardium was the single location showing a uniform presence of amyloid.

Summary and Conclusions

A case of cardiac amyloidosis with a 1,090-Gm. heart is presented in detail. This is believed to be the largest amyloid heart reported, especially since the heart represented 2.7 per cent of the patient's total body weight, or five times the normal.

Eighty-two cases from the literature and 20 cases of our own have been analyzed, and the literature on cardiac amyloidosis has been reviewed.

Most patients are men over 70 years of age, in poor nutritional state, who have predominantly intractable left ventricular failure, a systolic cardiac murmur, minimal coronary atherosclerosis, cardiomegaly (av. 452 Gm.), variably positive Congo-red tests, and cardinal involvement of the heart over other organs.

Electrocardiograms in 31 cases of cardiac amyloidosis are analyzed, and some useful correlations of special interest are made. Left axis deviation, parietal block, and a heart weight of 450 Gm. or more appear in a significant number of cases in which cardiac amyloidosis is the primary cause of death. Atrial fibrillation is frequently found in patients with cardiac amyloid with or without significant coronary atherosclerosis.

Acknowledgment

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References

1. Wilks, S.: Quoted by Dillon, J. A., and Evans, L. R.: Primary amyloidosis: A report of 3 cases. Ann. Int. Med. 17: 722, 1942.
2. Beneke, R., and Bönning, F.: Ein Fall von lokaler Amyloidose des Herzens. Beitr. path. Anat. 44: 362, 1908.
3. Lubarsch, O.: Zur Kenntnis ungewöhnlicher Amyliodablagerungen. Arch. Path. Anat. 271: 867, 1929.
4. Kann, G.: Ein Fall von isolierter Amyloidose des Herzens. Arch. Path. Anat. 137: 22, 1922.
5. Silver, H., and Lindblom, A. F.: Ein Fall von

allgemeiner Amyloidose ohne nachweisbare Ursache (sogenannte idiopathische Amyloidose). Acta med. scandinav. **64**: 529, 1926.

6. STEINHAUS, F.: Über eine seltene Form von amyloid-und hyalin Infiltration am Circulations und Digestionsapparat. Ztschr. klin. Med. **45**: 375, 1902.
7. WILD, C.: Beitrag zur Kenntnis der amyloiden und der hyalinen Degeneration des Bindegewebes. Beitr. path Anat. **1**: 175, 1886.
8. HIGGINS, W. H., AND HIGGINS, W. H., JR.: Primary amyloidosis: A clinical and pathological study. Am. J. M. Sc. **220**: 610, 1950.
9. LINDSAY, S., AND KNORP, W. F.: Primary systemic amyloidosis. Arch. Path. **39**: 315, 1945.
10. BARNARD, W. G., SMITH, F. B., AND WOODHOURSE, J. L.: Atypical amyloidosis with macroglossia. J. Path. & Bact. **47**: 311, 1938.
11. BURMCEKCI, K.: Mitteilung eines Falles von atypischer Amyloidose (paramyloidose). Arch. Path. Anat. **302**: 607, 1938.
12. CORNELIUS, H. V.: Zur Pathogenese der Paramyloidose, insbesondere im Herzmuskel. Ztschr, Kreislaufforsch, **41**: 57, 1952.
13. FREDERICKSEN, T.: Amyloidosis of the heart: A case of primary atypical amyloidosis exclusively localized to the heart. Ugesk. laeger **117**: 720, 1955.
14. GODOL, H. C.: So-called primary systemic amyloidosis probably due to myelomatosis. Acta med. scandinav. **160**: 431, 1958.
15. HASS, G .M., HUNTINGTON, R., AND KRUMDIECK, N.: The properties of amyloid deposits occurring in several species under diverse conditions. Arch. Path. **35**: 226, 1943.
16. KOLLER, F.: Über atypische Amyloidose als Ursache von Herzinsuffizienz. Schweiz med. Wchnschr. **62**: 522, 1932.
17. SOISALO, P., AND RITAMA, V.: Zur typischen Amyloidose mit besonderer Berucksichtigung des Herzens. Acta med. scandinav. **116**: 260, 1943.
18. VAN DER STRAETEN, MARCEL-VUYLSTEEK, K., AND DE VOS, L.: Hartamyloidose. Acta clin. belg. **9**: 169, 1954.
19. SMITH, J. M.: Primary (atypical) localized amyloidosis of heart: Case Report. U. S. Armed Forces M. J. **2**: 723, 1951.
20. RITIMA, V., AND SAKSELA, N.: Primary atypical amyloidosis due to allergic hyperglobulinemia. Ann. med. int. Fenniae **38**: 188, 1949.
21. WHITTLESAY, W. N.: Primary atypical amyloidosis, report of a case. Arch. Int. Med. **86**: 245, 1950.
22. REIMANN, H. A., KOUCKY, R. F., AND EKLUND, C. M.: Primary amyloidosis limited to tissue of mesodermal origin. Am. J. Path. **11**: 977, 1935.
23. FISHER, H., AND PREUSS, F. S.: Primary systemic amyloidosis with involvement of the nervous system. Report of Case. Am. J. Clin. Path. **21**: 758, 1951.
24. MULLIGAN, R. M.: Amyloidosis of the heart. A.M.A. Arch. Path. **65**: 615, 1958.
25. BANNICK, E. G., BERKMAN, J. M., AND BEAVER, D. C.: Diffuse amyloidosis: three unusual cases; a clinical and pathologic study. Arch. Int. Med. **51**: 978, 1933.
26. Case Records of the Massachusetts General Hospital: Case No. 36763. New England J. Med. **257**: 1185, 1957.
27. BINFORD, C. H.: Primary amyloid disease of the myocardium and blood vessels: Report of case with death from myocardial failure. Arch. Path. **29**: 314, 1940.
28. FINDLEY, J. W., JR., AND ADAMS, W.: Primary systemic amyloidosis simulating constrictive pericarditis with steatorrhea and hyperesthesia. Arch. Int. Med. **81**: 342, 1948.
29. LINDSAY, S.: The heart in primary systemic amyloidosis. Am. Heart J. **32**: 419, 1946.
30. PARKER, R. L., ODEL, H. A., LOGAN, A. H., JR., KELSEY, J. R., JR., AND EDWARDS, J. E.: Primary systemic amyloidosis: Report of 2 cases. M. Clin. North America **34**: 1119, 1950.
31. JOSSELSON, A. J., PRUITT, R. D., AND EDWARDS, J. E.: Amyloid localized to the heart: Analysis of 29 cases. A.M.A. Arch. Path. **54**: 359, 1952.
32. JOSSELSON, A. J., PRUITT, R. D., AND EDWARDS, J. E.: Amyloid disease of the heart. M. Clin. North America **34**: 1137-1144, 1951.
33. HULBERT, B., AND MEYER, H. M.: Primary amyloidosis of the heart. Am. Heart J. **38**: 604, 1949.
34. HOLZMANN, M.: Zur Herzamyloidose, mit besonderer Berücksichtigung des EKG-Befundes. Ztschr. Kreislaufforsch. **39**: 401, 1950.
35. WESSLER, S., AND FREEDBERG, A. S.: Cardiac amyloidosis: Electrocardiographic and pathologic observations. Arch. Int. Med. **82**: 63, 1948.
36. BALLINGER, J.: Amyloid heart disease. Am. J. M. Sc. **217**: 308, 1949.
37. THOMASHOW, A. I., ANGLE, W. D., AND MORRIONE, T. G.: Primary cardiac amyloidosis. Am. Heart J. **46**: 895, 1953.
38. JONES, R. S., AND FRAZIER, D. B.: Primary cardiovascular amyloidosis: its clinical manifestations, pathology and histogenesis. Arch. Path. **50**: 366, 1950.
39. BERNREITER, M.: Cardiac amyloidosis, electrocardiographic findings. Am. J. Cardiol. **1**: 644, 1958.
40. EISEN, H.: Primary systemic amyloidosis. Am. J. Med. **1**: 144, 1946.

41. KULEY, M., YALCIN, S., AND SENTURK, P.: Systemic amyloidosis: One case. Türktib. cem. mec. **20**: 260, 1954.

42. OHLIGER, P. H., AND HARMOS, O.: Intractable heart failure due to amyloidosis: Case Report, Mil. Surgeon **115**: 1, 1954.

43. WOOLF, C. R.: Primary systemic amyloidosis with gross cardiac involvement. South African M. J. **24**: 146, 1950.

44. RANSTROM, S.: Myocardial amyloidosis. Acta path. et microbiol. scandinav. **28**: 302-308, 1951.

45. BUDD, J. W.: Primary amyloid disease of the heart. Am. J. Path. **10**: 299, 1934.

46. COHEN, A. K.: Primary systemic amyloidosis, with report of a case. M. J. Australia **2**: 491, 1953.

47. DE WOLF, H., AND CLARKE, B. E.: Primary amyloidosis: Report of a case. Am. J. Clin. Path. **20**: 165, 1950.

48. FERRIS, H. W.: Amyloidosis of lungs and heart. Am. J. Path. **12**: 701, 1936.

49. HIRSCH, E. F.: Primary amyloidosis of the heart, kidneys and other viscera. Illinois M. J. **103**: 179, 1953.

50. HRUSKA, V.: Primary cardiac amyloidosis. Casop. lék. cesk. **93**: 1036, 1954.

51. SEIP, M.: Amyloidosis with cardiac involvement and macroglossia: Case. Tidsskr. norske laegefor. **70**: 341, 1950.

52. KERWIN, A. J.: Idiopathic amyloid disease of the heart. J. Lab. & Clin. Med. **22**: 255, 1936.

53. KOLETSKY, S., AND STECHER, R. M.: Primary systemic amyloidosis: involvement of cardiac valves, joints and bones, with pathologic fracture of the femur. Arch. Path. **27**: 267, 1939.

54. PEARSON, B., RICE, M. M., AND DICKENS, K. L.: Primary systemic amyloidosis: Report of 2 cases in Negroes, with special reference to certain criteria for diagnosis. Arch. Path. **32**: 1, 1941.

55. LOOGEN, F., AND BOHM, W.: Isolierte Amyloidose des Herzens. Ztschr. Kreislaufforsch. **43**: 224, 1954.

56. SAPPINGTON, S. W., DAVIE, J. H., AND HORNEFF, J. A.: Primary amyloidosis of the lungs. J. Lab. & Clin. Med. **27**: 882, 1942.

57. JACKSON, A., AND SLAVIN, M.: Primary amyloidosis: Report of 2 cases. Am. Heart J. **47**: 839, 1954.

58. STRICH, S. J., AND WADE, G.: Primary amyloidosis presenting with peripheral neuritis and intractable heart-failure. Lancet **2**: 70, 1953.

59. TREBEDI, B. P., AND ROY, A. R.: Primary systemic amyloidosis. J. Indian M. A. **23**: 24, 1953.

60. WAHI, P. N., AND TANDON, H. C. D.: Primary systemic amyloidosis. Indian M. Gaz. **85**: 537, 1950.

61. WARREN, S.: Generalized amyloidosis of the muscular systems. Am. J. Path. **6**: 161, 1930.

62. WILEY, A. T., TEETER, R. R., AND SCHNABEL, T. G.: Rupture of the spleen in primary amyloidosis: report of case. M. Clin. North America **35**: 1841, 1951.

63. WILLIAMS, A. W.: Primary amyloidosis with renal and myocardial failure. J. Clin. Path. **5**: 54, 1952.

64. RANSTROM, S.: Amyloidosis myocardii. Acta med. scandinav. **123**: 111, 1946.

65. HUSSELMANN, H.: Beitrag zum Amyloid-Problem auf Grund von Untersuchungen an menschlichen Herzen. Arch. Path. Anat. **327**: 607, 1955.

66. GOLDEN, A.: Primary systemic amyloidosis of the alimentary tract. Arch. Int. Med. **75**: 413, 1945.

67. IVERSON, L., AND MORRISON, A. B.: Primary systemic amyloidosis. Arch. Path. **45**: 1, 1948.

68. DAHLIN, D. C.: Primary amyloidosis, with a report of 6 cases. Am. J. Path. **25**: 105, 1949.

69. DILLON, J. A., AND EVANS, L. R.: Primary amyloidosis: A report of 3 cases. Ann. Int. Med. **17**: 722, 1942.

70. LEE, H. Y., AND KAUFMANN, W.: Cardiac amyloidosis in the aged. A.M.A. Arch. Path. **64**: 494, 1957.

71. LARSEN, R. M.: Pathological study of primary myocardial amyloidosis. Am. J. Path. **6**: 147, 1930.

72. PERLA, D., AND GROSS, H.: Atypical amyloid disease. Am. J. Path. **11**: 93, 1935.

73. HARTNEY, J. B., BIEDERMAN, A. A., BLUMBERG, J. M., AND LEEDHAM, C. L.: Primary systemic amyloid disease: Report of a case emphasizing cardiac involvement. Arch. Path. **47**: 598, 1949.

74. GRANT, R. P.: Left axis deviation. An electrocardiographic-pathologic correlation study. Circulation **14**: 233, 1956.

75. HASS, G., AND SCHULZ, R. Z.: Amyloid: Methods of isolating amyloid from other tissue elements. Arch. Path. **30**: 240, 1940.

76. HASS, G.: Studies of amyloid: The isolation of a polysaccharide from amyloid-bearing tissues. Arch. Path. **34**: 92, 1942.

77. HUEPER, W. C.: Arteriosclerosis: The anoxemia theory. Arch. Path. **39**: 187, 1945.

78. KING, L. S.: Atypical amyloid disease, with observations on a new silver stain for amyloid. Am. J. Path. **24**: 1095, 1948.

79. BLOCK, W. D., RUKAVINA, J., AND CURTIS, A. C.: Atypical electrophoretic peak in serum of patients with familial primary systemic amy-

loidosis. Proc. Soc. Exper. Biol. & Med. 89: 175, 1955.

80. SCHNECKLOTH, R. E., AND PAGE, I. H.: The nephrotic syndrome and chronic hypotension associated with primary systemic amyloidosis. Am. J. M. Sc. 230: 299, 1955.
81. BOCK, J.: Serum protein fractionation in normal old individuals. J. Gerontol. 3: 119, 1948.
82. HAHN, P. F., BAUGH, P., AND FOSTER, D. L.: Production of gastric ulcers in dogs on protein depletion regime. Proc. Soc. Exper. Biol. & Med. 95: 238, 1957.
83. KIRK, E., AND CHIEFFI, M.: Vitamin studies in middle-aged and old individuals. III. Thiamine and pyruvic acid blood concentrations. J. Nutrition 38: 353, 1949.
84. KIRK, J. E., AND CHIEFFI, M.: Vitamin studies in middle-aged and old individuals. III. The concentration of total ascorbic acid in whole blood. J. Gerontol. 8: 301, 1953.
85. MCLESTER, M. S., AND DERBY, W. J.: Nutrition and Diet in Health and Disease. Ed. 6. Philadelphia, W. B. Saunders Company, 1952, p. 602.
86. SINCLAIR, H. M.: Nutritional problems in the elderly. *In* Modern Trends in Geriatrics, edited by W. Hobson. New York, Paul B. Hoeber, Inc., 1957, p. 303.
87. DAHLIN, D. C., AND EDWARDS, J. E.: Cardiac clinics: Amyloid localized in the heart. Proc. Staff Meet., Mayo Clin. 24: 89, 1949.
88. DAHLIN, D. C., AND EDWARDS, J. E.: Classification and general aspects of amyloidosis. M. Clin. North America 34: 1107, 1950.

Infinity

Alike in the external and the internal worlds, the man of science sees himself in the midst of perpetual changes of which he can discover neither the beginning nor the end. If, tracing back the evolution of things, he allows himself to entertain the hypothesis that the universe once existed in a diffused form, he finds it utterly impossible to conceive how this came to be so; and equally, if he speculates on the future, he can assign no limit to the grand succession of phenomena ever unfolding themselves before him.—HERBERT SPENCER. *First Principles.* New York, reprinted from the Fifth London Edition, The Home Library, 1880, p. 57.

ABSTRACTS

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CONGESTIVE HEART FAILURE

Nordenson, N. G.: Cardiac Decompensation and Erythropoietic Function. Acta. med. scandinav. **166**: 327, 1960.

Erythropoietic function was studied in 43 subjects with mild congestive heart failure. Twelve subjects had polycythemia (increased hemoglobin, red cells, and hematocrit), but no increase in erythropoiesis in the bone marrow. In the remainder, there was increased erythropoietic function without peripheral polycythemia. The theoretical explanations for these findings are discussed briefly.

SHEPS

CORONARY ARTERY DISEASE

Antonis, A., and Bersohn, I.: Serum-triglyceride Levels in South African Europeans and Bantu and in Ischaemic Heart-disease. Lancet **1**: 998 (May 7), 1960.

A study was made of fasting serum-triglyceride levels in the 2 main racial groups living in South Africa: the European, whose diet is similar to that of the Western hemisphere with 40 per cent of calories from animal fat, and the Bantu whose diet contains less than 15 per cent of calories from fat and is high in carbohydrate. The majority of the young subjects of both races had values under 114 mg. per 100 ml. All the European premenopausal females had triglyceride levels below this value. A substantial number of European men and 96 per cent of the heart disease cases had serum-triglyceride concentrations greater than this. Serum-triglyceride levels of Bantu men and premenopausal European women showed no age trend. Values for European men showed a distinct age trend with a wide scatter. Ischemic heart disease patients at all ages had levels very much higher than those of young subjects but only slightly higher than a large proportion of older European men. The polyenoic-fatty-acid distribution for Bantu, women Europeans, and heart disease cases showed no variation with age. For male Europeans an inverse variation with age was shown in the percentage of dienoic fatty acids (linoleic acid). Ischemic heart disease cases had a lower proportion of all polyenoic fatty acids in their triglycerides than the other subjects.

KURLAND

Broch, O. J., and Ofstad, J.: The Post-myocardial-infarction Syndrome. Acta med. scandinav. **166**: 281, 1960.

In a retrospective study of 500 patients treated for myocardial infarction, the incidence of the post-infarction syndrome was about 1 per cent. These cases, as well as some drawn from other sources, make up a total of 8 patients presented in this brief review. Six patients had the usual syndrome of pericarditis, pleurisy, pneumonia, increased erythrocyte sedimentation rate, and fever. Two other patients developed arthritis about 3 weeks after an acute myocardial infarction. Anticoagulant therapy was continued in all these patients with no untoward results. No steroids were given, as the cases were mild to moderate in severity. The authors concur with

Dressler in suggesting that this illness may represent an allergic reaction on an auto-immune basis.

SHEPS

deLeon, A. C., Bellet, S., Tsitouris, G., Lecks, L. E., and Sandberg, H.: The Fibrinolytic System and Use of Fibrinolysin in Myocardial Infarction. Am. J. Cardiol. **5**: 674 (May), 1960.

Spontaneous fibrinolytic activity was not found in the plasmas of 28 normal persons nor in 30 patients with acute myocardial infarction. A significantly elevated level of antifibrinolytic activity was found among the infarction patients. Therefore, 10 patients whose infarction apparently was less than 3 days old were given fibrinolysin (Actase) infusions of 100,000 to 200,000 units daily for 1 to 4 days or more, aiming to promote dissolution of the coronary clot. Eight patients had sustained relief of cardiac pain, and 5 showed improvement in ST-T abnormalities that lasted as long as the fibrinolysin effect (2 to 3 days). Side effects from fibrinolysin were noted in 5 patients who developed fever as high as 103 F.; and chills, nausea, and slight hypotension were associated with some of these febrile episodes. It was thought that this type of therapy deserves further trial.

ROGERS

Givner, M. L., Bauld, W. S., Hale, T. R., Vagi, H. K., and Nilsen, M.: Effect of ACTH, CG and TP on Urinary Estradiol, Estrone and Estriol of Human Subjects with Previous Myocardial Infarction. J. Clin. Endocrinol. & Metab. **20**: 665 (May), 1960.

In many pathologic conditions, patients excrete a higher than normal proportion of estriol to total estrogens when treated with estrone. A previous study had shown that following administration of estradiol-17β, patients with previous myocardial infarction excreted more estriol relative to estrone and estradiol-17β than did a control group. The present investigation involved determination of the urinary estrogen pattern in patients with myocardial infarction after the administration of ACTH, chorionic gonadtropin and testosterone propionate. Five of the 6 myocardial infarction patients responded to injection of ACTH by excreting proportionately more estrone than estriol. Two control subjects were similar. Three of 4 myocardial infarction subjects excreted more estrone or estradiol-17β than estriol whereas 2 of 3 control patients did the opposite. The data suggest that following the injection of ACTH, chorionic gonadotropin and testosterone propionate proportionately more estrone than estriol was excreted. However, following the injection of testosterone proportionately more estradiol-17β than estrone in estriol was excreted. Of 12 myocardial infarction patients, only 2 responded by excreting more estriol than estrone. It is suggested that at present, the estrogen metabolic "defect" in myocardial infarction can be demonstrated only when estradiol-17β is administered.

KURLAND

Groover, M. E., Jr., Jernigan, J. A., and Martin, C. D.: Variations in Serum Lipid Concentration and Clinical Coronary Disease. Am. J. M. Sc. **239**: 133 (Feb.), 1960.

Since 1950 civilian executives and General officers with the United States Air Force have been part of an executive health program. Of these subjects, 177 had had 6 or more cholesterol determinations yearly for at least 5 years. The most characteristic factor noticed in this study was the variation in serum lipids. These were confirmed in 3 laboratories using aliquots of the same serum. There was a 25 per cent variation above the average in individuals who had no clinical evidence of heart disease. The variations in serum cholesterol seemed to be more closely related to clinically recognized coronary artery disease than was the 5-year average. Among 16 individuals with myocardial infarction, a period of abnormal fluctuation preceded each attack. For the most part these variations were usually above the 5-year average. The authors considered these variations in serum cholesterol concentration of such serious import that patients were often hospitalized until the lipid picture stabilized. The effect of emotional stress on increasing serum lipid values was also discussed.

SHEPS

Heller, E. M.: Levarterenol (Levophed) Therapy in Acute Myocardial Infarction. Canad. M.A.J. **82**: 917 (Apr. 30), 1960.

Levarterenol was considered to be the drug of choice for combating hypotension in acute myocardial infarction. Its use was advocated when the systolic blood pressure fell below 80 to 85 mm. Hg. regardless of whether other signs of shock were present. The method of administration was described, and the importance of close supervision of the patient, preferably by a special nurse, was emphasized. In fact, the only contraindication to the use of the agent was thought to be lack of adequate patient supervision. The prognosis seemed poorer when larger amounts of levarterenol were needed, but recovery was observed in a patient requiring the drug for 3 weeks and in concentrations as high

as 7 ampules (56 mcg. of levarterenol bitartrate) per 1,000 ml. of glucose solution.

ROGERS

James, T. N., and Brown, R. W.: Myocardial Infarction in Young Adults. Dis. Chest **37:** 430 (Apr.), 1960.

The authors have compared 27 patients from a veterans' hospital with 16 patients from a private hospital, all of whom were 35 years of age or younger and had myocardial infarction. In the veterans' group 21 of 27 patients developed myocardial infarction without pertinent associated disease such as diabetes, hypertension, or hypercholesteremia, but in 9 of 16 patients in the private hospital group, 1 of these diseases was present. In 7 of the 9 patients from both groups who died from myocardial infarction, 1 of these associated diseases was present. Four women were included in the private hospital series; each of these patients had an associated pertinent disease. The authors suggest that the age limit for the "young" adults for studies in myocardial infarction be set at 35 years.

KAYDEN

Johansson, B., Haeger, K., and Wallgren, G. R.: Studies of the Coronary Circulation. VI. Electrocardiographic Observations in Dogs Subjected to Coronary Artery Occlusion with Subsequent Implantation of Plastic Tubes to Supply the Ischemic Myocardium. Acta cardiol. **15:** 1, 1960.

Acute or subacute coronary occlusion was established in dogs either by insertion of a magnesium-aluminum needle or by high arterial ligation. Some of these dogs served as control animals, others were subjected to a sham operation, and a third group was subjected to implantation of a plastic tube carrying blood from the internal mammary artery directly to the myocardium. Electrocardiographic patterns suggestive of myocardial infarction were recorded in most dogs. In some animals, however, in spite of proved extensive myocardial damage there were no changes in the postoperative electrocardiogram. This was especially true when the right coronary artery was occluded. There were no signs of improvement in the electrocardiogram when a plastic tube carrying oxygenated blood was inserted adjacent to the infarcted area.

BRACHFELD

Malach, M., and Rosenberg, B. A.: Acute Myocardial Infarction in a City Hospital. III. Experience with Shock. Am. J. Cardiol. **5:** 487 (Apr.), 1960.

Of 264 patients with acute myocardial infarction observed during the year ending June 30, 1955, 25 had severe shock. Twenty of these were older than 60 years, 13 had been hypertensive, and 8 had a history of congestive heart failure. Shock followed the onset of the infaret by less than 48 hours in 11 patients and by 2 days to 4 weeks in the remainder. Norepinephrine therapy in 17 patients produced a pressor effect in 10 and a relief of shock in 7. Phenylephrine alone or 5 per cent dextrose infusion in 8 patients produced a pressor effect in 3 but relieved shock in none. All patients died within a maximum of 12 days after developing shock. The unfavorable outcome of this group, as compared to survival in 59 per cent of 183 reported cases of myocardial infarction with shock, was attributed to the present patients being older, sicker, and slower to obtain medical attention. Early therapy of shock with norepinephrine was advocated.

ROGERS

Maling, H., Highman, B., and Thompson, E. C.: Some Similar Effects after Large Doses of Catecholamines and Myocardial Infarction in Dogs. Am. J. Cardiol. **5:** 628 (May), 1960.

The effects of administering norepinephrine in saline, 0.51 to 0.85 mg. per Kg., or epinephrine in oil, 1 mg. per Kg., were compared in dogs with the effects of ligating the anterior descending coronary artery. Subsequent pronounced elevations of serum transaminases, lactic dehydrogenase, and alkaline phosphatase were observed in all 3 groups of dogs. Fatty myocardial changes, including increased triglyceride content, and hyperexcitability lasted approximately 4 days after catecholamine treatment and lasted 10 to 14 days after coronary occlusion. Pretreatment with phenoxybenzamine, an antiadrenergic agent, prevented the myocardial damage and most of the enzyme alterations in dogs infused with norepinephrine but not in those having coronary ligation. It was suspected that epinephrine released from the adrenal medulla during various stresses might contribute to some increases in serum enzyme levels noted clinically.

ROGERS

Malmros, H., and Borgstrom, S.: Mortality caused by Coronary Disease in Sweden. Ztschr. Kreislaufforsch., **49:** 201 (Mar.), 1960.

If international statistics concerning coronary disease mortality are to be compared, information must be available on the precision with which the diagnosis is made. For this purpose, all persons declared as having died of coronary disease on their death certificates in Sweden during the last quarter of 1956 were traced. Of the 3,221 cases where autopsy or electrocardiographic findings were available, the diagnosis was found reliable

in 77 per cent and probable in 9 per cent of the patients.

LEPESCHKIN

Plotz, H.: The Treatment of Angina Pectoris with a New Prolonged Action Pentaerythritol Tetranitrate. Am. J. M. Sc. **239**: 194 (Feb.), 1960.

The clinical experience in using a new sustained action Pentaerythritol tetranitrate (PETN) is described. This capsule contains many tiny pellets of PETN. The pellets are especially coated with a plastic semi-permeable membrane that requires only moisture to dissolve them. The medication is released by a leeching process over 8 to 10 hours providing effective drug levels for 12-hour periods. This capsule was administered twice daily in most of the 50 patients studied. Seventy-six per cent of these patients had considerable relief from angina; all had a reduction of at least one third in the number of nitroglycerin tablets required, and all had greater relief with the new preparation than with the 10 to 20 mg. tablets of PETN previously available. A few patients with mild angina did not require additional nitroglycerin, but many subjects were more comfortable with supplementary nitroglycerin. In general, side effects were transient and negligible.

SHEPS

Pojer, J., Sevela, M., Ninger, E., and Tovarek, J.: Enzymatic Pattern in Myocardial Infarction. Cardiologia **36**: 145, 1960.

Repeated determinations of 7 enzymes playing an important role in glycolysis and the Krebs cycle were performed in 50 patients with acute myocardial infarction: phosphoglucomutase, phosphohexose isomerase, aldolase, lactic dehydrogenase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, and malic dehydrogenase. Glutamic oxalacetic transaminase, lactic, and malic dehydrogenases, and phosphohexose isomerase proved to be about equally sensitive indicators of myocardial necrosis. Aldolase was less sensitive, and phosphoglucomutase and glutamic pyruvic transaminase were not suited for practical diagnosis. In one half of the patients an increased level of serum lactic dehydrogenase was found after glutamic oxalacetic transaminase had returned to normal. The same was observed in 4 of 21 patients in regard to malic dehydrogenase. In some patients glutamic pyruvic transaminase showed increased activity in the later course; this observation, however, cannot be considered a direct result of myocardial necrosis.

BRACHFELD

Seim, S.: Angina Pectoris. Acta med. scandinav. **166**: 255, 1960.

Long-term observations are recorded on a large number of Norwegian patients with angina pectoris. The first group consisted of 217 men and 143 women, all of whom had a normal electrocardiogram at rest. The second group included 176 men and 67 women in whom the electrocardiographic standard limb leads revealed pathologic changes. The minimum follow-up period was 5 years, and the maximum 25 years. These patients were all seen in the private practice of 1 internist. Survivorship data and curves were calculated for both sexes. The average mortality rate for all the men (groups 1 and 2 combined) was 7.9 per cent in the first year, and thereafter varied from 4 to 6.3 per cent over the next 8 years. Over the subsequent 6 years the mortality rate was somewhat less. Among the women in both groups, the mortality rate in year 1 was 7.1 per cent and then varied from 2.2 to 6.2 per cent over the subsequent 8 years. Thereafter the mortality rate was a little lower until the fifteenth year, when it was 7.6 per cent. When calculated separately, the second group of patients had a distinctly poorer prognosis. Mortality among the women in group 2 was particularly poor. This was probably related to the relatively small number in the total population, and also to their average age being some 5 years greater than the men or the women in group 1 at onset. Sixty-one per cent of the subjects sought medical attention within a year of the onset of their symptoms. A history of previous myocardial infarction worsened the prognosis in men. Elevation of the initial blood pressure seemed adversely to influence the prognosis in both men and women in group 2 but there was no appreciable difference in survivorship in group 1. Sixty-two per cent of the patients had died at the time the series was closed. Acute myocardial infarction and sudden death accounted for 40 to 43 per cent of the deaths. The remainder died of "chronic heart disease," cerebrovascular accidents, and other miscellaneous causes.

SHEPS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Burch, G. E., DePasquale, N., and Malaret, G.: Problems in Electrocardiography. Ann. Int. Med. **52**: 587 (Mar.), 1960.

A group of 10 patients were studied and the electrocardiographic diagnoses were compared with the findings of autopsy. The limitations of electrocardiographic interpretation were stressed. The first 3 patients demonstrated the difficulties

and inadequacies of the electrocardiographic interpretations concerning hypertrophy of the heart. In 2 patients with cerebrovascular lesions, the abnormalities in the electrocardiograms were probably produced by the cerebral injury, although the mechanism for these changes is unknown. The inability to diagnose myocardial infarctions from the electrocardiogram and the electrocardiographic diagnosis of myocardial infarction in the absence of this condition is illustrated in other patients. The authors stress the value of correlating electrocardiographic diagnoses with postmortem findings.

KAYDEN

Freiman, A. H., Tolles, W., Carbery, W. J., Ruegsegger, P., Abarquez, R. F., and LaDue J. S.: The Electrocardiogram During Exercise. Am. J. Cardiol. 5: 506 (Apr.), 1960.

A method has been developed for monitoring and recording electrocardiograms from several leads during a variety of physical activities. It was designed for use during flight and was extended to the study of the heart in health and disease. The technic employed pliable stainless-steel mesh electrodes and special electrode jelly or compound, which gave greater baseline stability for longer periods of time. The signal was monitored oscilloscopically and recorded on 2-channel paper or on magnetic tape. Somatic muscle potentials or other interference developing in association with exercise usually could be largely eliminated by appropriate filtering, either of the immediate signal or of that from the tape. The electrocardiograms so obtained were of sufficient technical quality to permit evaluation of ischemic-type changes in QRS, ST, and T areas.

ROGERS

Giraud, G., Latour, H., Puech, P., and Dermenghem, M.: Use of Dye Dilution Curves During Cardiac Catheterization. Arch. mal. coeur **53:** 77 (Jan.), 1960.

The dye concentration at the ear lobe was recorded continuously by means of a photo cell after rapid injection of 3 to 4 ml. of 1 per cent methylene blue through an intracardiac catheter previously filled with the dye. The values obtained with this method were shorter and showed a much narrower range of normal variability than when the catheter was not previously filled with dye. The appearance time (AT), measured from the beginning of injection into the pulmonary artery to the beginning of the ascent of the absorption curve, was 5 to 5.5 seconds in normal adults and 3.5 to 4 seconds in children. The duration of the ascent to the peak concentration time (CT) was 6 seconds, the disappearance time (DT) from the peak to the end of the descent was 10 to 12 seconds, and the recirculation time (RT) between the apices of the first and second peaks was 14 to 20 seconds. In 50 patients with mitral stenosis these values were compared with the mitral valve area determined during commissurotomy. An area exceeding 1.5 cm.^{2} corresponded to a normal AT and an increase not exceeding 2 and 4 seconds respectively for CT and DT. An area of 1 to 1.5 cm.^{2} corresponded to an increase of 0 to 2 seconds for AT, 0 to 4 seconds for CT, and 2 to 6 seconds for DT, while an area of 0.4 to 1 cm. corresponded to increases of 2 to 7, 2 to 4, and 2 to 7 respectively. When atrial fibrillation or marked mitral regurgitation was present, these increases were much greater, regardless of the mitral valve area, and the amplitude of the first peak was very low. Of the 50 cases of miscellaneous heart disease studied, primary pulmonary hypertension and chronic cor pulmonale showed marked delay of AT, CT, and DT. Ebstein's disease showed, in addition, a very low first and absent second peak. Left-to-right shunts were characterized by a shortened AT, normal CT, and greatly prolonged DT, while right-to-left shunts showed a very short AT with a double summit of the first peak, and prolonged CT and DT, when injection was made proximal to the shunt.

LEPESCHKIN

Goodyer, A. V. N., Chetrick, A., and Huvos, A.: Ear Oximeter for Cardiac Output Measurement. Yale J. Biol. & Med. **32:** 250 (Feb.)., 1960.

The accuracy of dye-dilution curves obtained with an ear oximeter have been questioned because the curves frequently differ from those obtained simultaneously from a systemic artery. Photometric characteristics of the earpiece system have not previously been given full consideration and methods of calibration have been inadequate. The Waters earpiece system was used to record 49 dye-dilution curves in normal subjects. Evans blue was injected into the right atrium via a venous catheter. Twenty-eight of these 49 curves had more prolonged downstrokes and less prominent recirculation peaks than curves obtained by direct fractional collection from a femoral artery. The criteria required for a satisfactory curve include absence of major irregularities of the curves or of their preliminary baseline; a primary peak greater than 20 mm. (equivalent to an arterial dye concentration of more than 6 mg.); and disappearance of the slope of the log replot clearly defined as a straight line for at least 4 seconds with a numerical value larger than 0.14 (the minimum slope found in the directly sampled arterial curves). With these criteria 18 earpiece curves in this study were rejected. An error of

less than ± 13 per cent was observed when this method was used to determine the proportionate change of cardiac output in the same resting or exercising subject, provided the placement of the earpiece was unchanged. Discrepancies were attributed to inadequacy of the ear pinna as a system for rapid and continuous sampling of dye-color in arterial blood. The validity of earpiece curves in estimating cardiac output depended greatly on the exclusion of curves that were not representative of those expected or simultaneously observed in a major artery. The arbitrary criteria used to designate "satisfactory" curves may be expected to result in rejection of about 35 per cent of all recorded earpiece curves. In patients with enlarged hearts this loss of data will increase and in these instances it will be necessary to validate at least 1 earpiece curve of each subject by direct comparison with a simultaneous arterial sample indicator-dilution curve.

LEVINSON

Hartman, H.: The Jugular Venous Tracing. Am. Heart J. **59**: 698 (May), 1960.

In this article the shape of the venous tracing, the significance and derivation of each of its components, and the usefulness of the venous tracing as a reference tracing for the phonocardiogram are discussed and illustrated in various cardiac disorders.

SAGALL

Lepeschkin, E., Marchet, H., Schroeder, G., Wagner, R., dePaula e Silva, P., and Raab, W.: Effect of Epinephrine and Norepinephrine on the Electrocardiogram of 100 Normal Subjects. Am. J. Cardiol. **5**: 594 (May), 1960.

Seven-lead electrocardiograms were recorded by a direct-writing machine during infusions of epinephrine or norepinephrine, 0.1 to 0.3 meg. per Kg. per minute, in 100 healthy young adults, 33 of whom were pregnant. Epinephrine increased the heart rate except in those having a great hypertensive effect, increased QRS amplitude, produced slight descending depression of the S-T segment, lowered the T wave, and caused the U wave to appear earlier and in larger form. The latter 3 changes were related to quickening of the initial phase of repolarization and slowing of the terminal phase, and they have been suppressed by administering potassium. These changes may be indistinguishable from those caused by coronary artery disease. Norepinephrine slowed the heart rate as the blood pressure increased, heightened QRS amplitude and usually elevated the T wave. However, after atropine (or in the isolated heart) its effect was similar to that of epinephrine, so it was believed that the difference between the effects of the 2 drugs could be largely attributed to reflex autonomic changes derived from norepinephrine's stimulation of pressoreceptors. Ectopic rhythms or atrioventricular block was observed in 28 patients receiving norepinephrine, chiefly at higher levels of blood pressure, and in 15 patients receiving epinephrine, at various levels of blood pressure and heart rate.

ROGERS

Niggli, S., and Wuhrmann, F.: On the Electrocardiogram in Dehydration. Cardiologia **36**: 162, 1960.

Electrocardiograms observed in 7 cases of severe dehydration and marked hemoconcentration are described. A characteristic feature is the temporary appearance of "P-pulmonale." The significance of the observed changes is briefly discussed.

BRACHFELD

Schmitt, W., and Braun, H.: Results of Ultrasonic Cardiography in Persons with Normal Hearts and with Mitral Disease. Ztschr. Kreislaufforsch. **49**: 214 (Mar.), 1960.

The calibrated ultrasonic cardiogram was registered in the region of absolute cardiac dullness, together with the heart sounds and the electrocardiogram, in 44 patients with normal hearts, 42 patients with mitral stenosis and 19 patients with mitral insufficiency. The normal ultrasonic cardiogram, corresponding to movement of the left atrial wall, consists of a peak (1) after the P wave, a nadir (2) after QRS, a slow ascent to a kink (3) at the end of T, a sharp ascent to a peak (4) corresponding to opening of the mitral valve, and a sharp descent to another kink (5) at the beginning of the diastolic plateau. In normal persons the descent 4-5 corresponded to a velocity of the left atrial wall of 56 to 137 mm./second, while in all patients with mitral stenosis this velocity was smaller. In mitral insufficiency, this velocity was greater than in normal individuals (80 to 180 mm. per second) but there was no sharp boundary between the 2 groups. The ascent 2-3 in mitral insufficiency was also much steeper than in normal persons and the kink 3 less pronounced. The velocity of movement during the descent 4-5 was found to have a direct relation to the mitral valve area measured during operation or at autopsy. Ultrasonic cardiography is therefore an important and accurate method in the preoperative differentiation between predominant mitral stenosis and insufficiency and the recognition of renewed stenosis after valvulotomy.

LEPESCHKIN

Young, E., Liebman, J., and Nadas, A. S.: The Normal Vectorcardiogram of Children. Am. J. Cardiol. **5**: 457 (Apr.), 1960.

Vectorcardiograms were obtained by a modified Grishman cube technic from 135 children clinically free of heart disease, aged 2 through 14 years. No significant difference was found between the records from those aged 2 through 5 and the older children, so all tracings were analyzed as 1 group. The normal QRS and T patterns in 3 planes were described and were considered to be very specific, although many minor variations were noted. The findings were qualitatively similar to those in adults but quantitative comparison was not possible because of the lack of a comparable study in adults. The average total QRS duration of 0.061 second in children contrasted with the 0.095 second figure found in adults by one of the authors.

ROGERS

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Ginsburg, I., Laufer, A., and Rosenberg, S. Z.: Cardiac Lesions Produced in the Rabbit by Intramyocardial Injection of Various Microorganisms. Brit. J. Exper. Path. **41**: 19 (Feb.), 1960.

Histopathologic changes obtained in the rabbit's heart by a single intramyocardial injection of hemolytic streptococci were studied. Endomyocarditis, muscle necrosis, and a marked granulomatous reaction were noted. Such lesions were not specific for hemolytic streptococci. Neither trauma alone nor the intravenous injection of hemolytic streptococci alone caused pathologic lesions in the heart. Well-developed lesions appeared in the heart when the intravenous injection of these organisms was preceded by myocardial puncture with a sterile needle. Thus, myocardial trauma appeared to be essential for the production of myocardial changes provided that streptococci were present in the blood.

KALMANSOHN

Hack, H. J., and Schneider, K. W.: The Question of So-called Idiopathic Cardiac Hypertrophy. Ztschr. Kreislaufforsch. **49**: 223 (Mar.), 1960.

Three patients (22, 31, and 68 years old) died with the clinical signs of severe cardiac failure; hypertension was never present. Autopsy showed marked hypertrophy of both ventricles without any pathologic changes in the valves or the great vessels. All 3 patients showed multiple fibrous scars, and the myocardial hypertrophy could be considered as compensatory for the impairment of the contractile force by the scar tissue. One patient showed also islands of cellular infiltration with occasional giant cells, so that the fibrosis in this case could be definitely attributed to a myocarditis subsequent to repeated treatment with erysipelas serum. One other patient could also have had myocarditis as a result of repeated tonsillitis, while the third patient had no infections in his history. The designation of "so-called idiopathic myocarditis" must accordingly be retained for cases where the etiology cannot be determined with certainty.

LEPESCHKIN

Hill, R. W., and Bayrd, E. D.: Phagocytic Reticuloendothelial Cells in Subacute Bacterial Endocarditis with Negative Cultures. Ann. Int. Med. **52**: 310 (Feb.), 1960.

The records of 273 patients with subacute bacterial endocarditis in whom blood smears were available, were studied. The period of observation was 15 years. Blood cultures of 228 of these patients were positive. The examination of the blood smears revealed that 176 of these 228 patients did not have any reticuloendothelial cells of the phagocytic type. The other 52 patients did exhibit reticuloendothelial cells, which were actively phagocytic in 19 instances. The blood cultures of 45 patients were consistently sterile. Blood smears in 15 of these patients showed reticuloendothelial cells, and active phagocytosis was noted in 12 of these 15 patients. The number of reticuloendothelial cells tended to be greater in patients with sterile blood cultures, when contrasted not only to those with positive cultures but also to those who had diseases that might be confused with subacute bacterial endocarditis. In 5 of 13 patients with subacute bacterial endocarditis and sterile blood cultures, the blood urea nitrogen was elevated. The number of reticuloendothelial cells and the amount of active phagocytosis tended to be greater in this group. It is suggested that when the number of these cells exceeds 9 per cent of the differential count of a patient with obscure fever and sterile blood cultures, that treatment for subacute bacterial endocarditis be given until the diagnosis is proved otherwise.

KAYDEN

Kline, I. K., and Saphir, O.: Chronic Pernicious Myocarditis. Am. Heart J. **59**: 681 (May), 1960.

With a review of the literature and a presentation of 6 new cases the authors call attention to a type of chronic myocarditis for which the term "pernicious myocarditis" seemed appropriate. This type of myocarditis was not a specific anatomic entity, but in the author's geographic area (Illinois) a chronic form of isolated myocarditis

of obscure etiology was the most common cause. This pernicious myocarditis clinically and pathologically resembled chronic Chagas' myocarditis, but no parasites were found. The clinical features of these cases consisted mainly of progressive myocardial failure with a protracted relentless downhill course, often culminating in unexpected death. At autopsy all cases showed a large heart with no changes in the endocardium or pericardium. Microscopic examination showed a chronic, mainly interstitial, myocarditis with young connective tissue compressing and eventually replacing heart muscle fibers and interstitial infiltration of inflammatory cells. The importance of recognizing pernicious myocarditis lay in the fact of its grave prognosis and fatal outcome, despite occasional temporary periods of remissions.

SAGALL

HYPERTENSION

Connor, T. B., Thomas, W. C., Jr., Haddock, L., and Howard, J. R.: Unilateral Renal Disease as a Cause of Hypertension: Its Detection by Ureteral Catheterization Studies. Ann. Int. Med. 52:544 (Mar.), 1960.

The demonstration that renal ischemia can produce hypertension in experimental animals and that in man, reduced arterial flow to 1 kidney may produce a clinical picture indistinguishable from essential hypertension, has stimulated a search for a method which will identify the diseased kidney. The present study indicates that analysis of simultaneously collected urine from each kidney in hypertensive subjects is a valuable guide in distinguishing those abnormal kidneys that are responsible for hypertension from those that are not. In 9 patients with at least a 50 per cent reduction in urine volume from 1 kidney and a 15 per cent or more reduction in sodium concentration on this same side, striking relief of hypertension followed surgical procedures. In 8 other patients with radiographic evidence of unilateral renal disease, in whom the catheterization study showed a lowering of urine volume from the diseased kidney, but in whom sodium concentrations were equal or greater from the side with the lesser volume, nephrectomy did not alter the blood pressure. Renal arteriography is helpful in evaluating catheterization studies and in determining the choice of surgical procedure for the relief of hypertension. The authors believe that the functional pattern of reduced arterial flow to 1 kidney as demonstrated by ureteral catheterization studies correlated well with the anatomic evidence of renal ischemia and the response of the patients' blood pressure to nephrectomy.

KAYDEN

Dunsmore, R. A., Dunsmore, L. D., and Elias, M: The Use of Syrosingopine (SU-3118) and Hydralazine in Ambulatory Hypertensive Patients. Am. J. M. Sc. 239: 148 (Feb.), 1960.

Syrosingopine was administered to 64 hypertensive patients. A blood pressure response was noted with as little as 0.25 mg., but most patients demonstrated significant reduction in blood pressure only on a daily dose between 4 and 8 mg. Doses above these levels were shown to have increased pharmacologic side effects without additional antihypertensive activity. The side effects noted were the same as those with Reserpine. While 32 per cent of 34 patients had had side effects on Reserpine, only 9 per cent of these had side effects on Syrosingopine. This occurred without sacrifice of antihypertensive activity. Thirty-nine patients inadequately controlled with Syrosingopine had Hydralazine added to their treatment schedule. By the use of placebo studies, a definite synergistic action was demonstrated between these 2 agents. Syrosingopine has a definite place in the therapy of hypertension in that it is as effective as Reserpine with fewer side effects.

SHEPS

Gardner, D. L.: The Relationship between Intermittent Hypotension and the Prevention by Hydralazine of Acute Vascular Disease in Rats with Steroid Hypertension. Brit. J. Exper. Path. 41: 60 (Feb.), 1960.

Systemic hypertension developed in albino rats treated with salt and cortexone (desoxycortone acetate). Subsequently the small arteries became the site of a focal segmental necrotizing arteritis. These lesions were usually accompanied by a widespread focal arteriolitis often involving the afferent glomerular arterioles, and by the presence of a subintimal material with the staining properties of fibrinoid. When rats were subjected to the same regimen with the addition of increasingly large amounts of hydralazine being injected simultaneously, neither form of vascular lesion developed over observation periods of as long as 3 months. The injections of hydralazine caused severe daily fluctuations in both systolic and diastolic blood pressures. It is suggested that the necrotizing arteritis and the fibrinoid arteriolar disease of experimental rat hypertension are related phenomena and that intermittent hydralazine prevents their development. Caution must be exercised before translating the significance of these results to other animal species.

KALMANSOHN

Genest, J., Dufault, C., Pigeon, G., Davignon, J., Bison, P., and Trudel, J.: Studies on a New Hypotensive Agent: Bretylium Tosylate. Canad. M. A. J. 82:872 (Apr.), 1960.

Forty-one hypertensive patients of mean age 49 years were given bretylium tosylate (Darenthin) in daily doses of 400 to 2,700 mg. for periods ranging up to 24 weeks. Bretylium was not pushed to tolerance; when a dose of 1,500 mg. per day failed to lower the blood pressure satisfactorily, other drugs were given additionally. Standing blood pressure readings were lowered an average of 24/15 mm.Hg by bretylium alone, 34/25 mm.Hg. when a thiazide was added, and 90/42 mm.Hg. when both a thiazide and hydralazine were added. Recumbent readings decreased slightly or insignificantly. Side effects apparently were noted in most patients but generally were mild and included principally dizziness in 12, orthostatic hypotension in 10, digestive complaints in 9 and decreased sexual potency in 6; in 5 patients these difficulties required discontinuing bretylium. Parasympatholytic side effects were nil, since this agent has been found to exert a highly selective blocking effect on peripheral sympathetic nerves.

ROGERS

Geschickter, C. F., and O'Malley, W. E.: Production of Hypertension by Means of Injection of N,N′-Diemethyl-P-Phenylenediamine. Am. J. Clin. Path. **33**:281 (Apr.), 1960.

In a group of 13 dogs, the hypertensive effects of N,N′-dimethyl-p-phenylenediamine (Alarmine) were studied after unilateral nephrectomy. Alarmine produced hypertension only in the 7 nephrectomized dogs when this drug was injected directly into the contralateral renal artery. Blood pressure began to rise immediately in these animals and and reached a peak level in approximately 1 week. The values remained elevated for the 6 months of study. There were no toxic manifestations following injection. No changes in blood urea nitrogen or in hematocrit levels were noted 1 month after injections of Alarmine into the renal artery. No distinct lesions attributable to Alarmine could be detected in biopsies of the kidneys. It is suggested that a single transient insult to the renal substance in the presence of reduced renal mass can elicit a progressive and long-term effect on the cardiovascular system without concurrent measurable chemical or microscopic alterations.

KAYDEN

Kattus, A. A., Jr., Longmire, W. P., Cannon, J. A., Webb, R., and Johnston, C.: Primary Intraluminal Tumor of the Aorta Producing Malignant Hypertension: Successful Surgical Removal. New England J. Med. **262**: 694 (Apr. 7), 1960.

A 22-year-old woman presented a clinical picture of coarctation of the aorta and malignant hypertension of the Goldblatt-kidney type. At thoracotomy a primary intraluminal tumor of the aorta was found and successfully removed. The tumor, which was of mesenchymal origin, occluded just beyond the aortic arch producing the physical signs of coarctation of the aorta. Projections from the long tail of the tumor extended into the orifice of the renal arteries causing renal ischemia and the clinical features of malignant hypertension. Successful surgical removal of the growth and its extensions resulted in complete resolution of the hypertensive disease. This case is believed to be the first reported in the literature of successful surgical removal of a primary intraluminal tumor of the aorta.

SAGALL

Lewis, J.: Clinical Experience with Bretylium Tosylate. Canad. M.A.J. **82**: 877 (Apr. 23), 1960.

The short-term effects of antihypertensive therapy with bretylium tosylate in 10 patients were described briefly. Daily dosage of 600 to 3300 mg. was employed, and other antihypertensive drugs were used in 6 patients. Substantial blood pressure lowering in the upright position (from sympathetic nerve inhibition) was achieved in 8 patients, while the recumbent readings were lowered appreciably in only 2. Annoying side effects were observed occasionally, but seldom was there constipation, urinary hesitancy, or impotence. It was thought that bretylium represented a significant advance in the treatment of hypertension because it was effective and relatively well tolerated.

ROGERS

Maronde, R. F., Barbour, B., and Frasher, W.: Intravenous Mecamylamine (Inversine) as a Means of Determining the Effective Oral Dosage. Am. J. M. Sc. **239**: 154 (Feb.), 1960.

Intravenous Mecamylamine was administered to 11 hypertensive patients. The solution consisted of Mecamylamine in 5 per cent glucose in water in a ratio of 1 mg. per 5 ml. The rate of infusion was approximately 0.5 mg. of Mecamylamine per minute. Supine and standing blood pressures were determined every 5 minutes. The infusion was terminated when a standing pressure of 140/90 was reached, or if a maximum of 90 mg. of Mecamylamine was given. Only 1 patient received the latter dose and he manifested no blood pressure response. An oral dose similar to the total amount of Mecamylamine administered intravenously was then given orally once daily for 24 to 72 hours after the intravenous infusion and subsequently this same dose was given every 12 hours. There was some lability of the blood pressure for 24

to 72 hours after the intravenous infusion and because of this the initial daily dose of Mecamylamine was less than the subsequent requirements.

SHEPS

Tennant, R. A., and Leslie, D. W.: Chlorothiazide in the Treatment of Pre-eclamptic Toxaemia and Essential Hypertension. Scottish M. J. **5**: 113 (Mar.), 1960.

Five hundred and eighty-eight cases of pre-eclamptic toxemia were admitted to hospital over a 16-month period. Labor was induced in those at or beyond the thirty-eighth week of pregnancy. In the remainder, a period of observation of 48 to 72 hours was instituted, during which time the patient was kept at rest and under sedation. In the majority of patients the blood pressure fell, urinary output increased and edema disappeared. Where the signs of pre-eclamptic toxemia persisted, namely a blood pressure of over 140/90 mm. of Hg at rest in bed, chlorothiazide was administered. This was given as a 4-day course of 2 Gm. daily each week as long as pregnancy was allowed to continue. Serum sodium and potassium were determined weekly and subclinical potassium deficiency occurred once. Forty cases of pre-eclamptic toxemia were treated with this program. In 38 patients weight loss occurred and was associated with relief of symptoms. The edema disappeared and the blood pressure tended to fall. The effect on albuminuria was inconstant. Where no weight loss occurred the signs and symptoms were unaffected and 1 of these patients developed eclampsia. Many of the patients gained between 2 and 4 lbs. during the weekly "rest period." In most patients there was a gain to the fetus in respect to maturity. Fourteen patients with essential hypertension were also treated; 5 in conjunction with hypotensive drugs. Weight loss usually occurred but this was not as uniform or as marked as in the toxemia cases. The blood pressure fell in all patients.

SHEPS

White, F. N., Sambhi, M. P., and Grollman, A.: Renal Function in Hypertensive Cardiovascular Disease of Rat. Am. J. Physiol. **198**: 221 (Feb.), 1960.

Rats were rendered hypertensive by subjecting them for a period of several weeks at the time of weaning to a choline-free or potassium-free diet. Urea clearance, renal blood flow, and tubular mass of the chronically hypertensive animals remained normal. Only the glomerular filtrate rate was significantly reduced in the hypertensive animals reflecting the changes in the glomerular membrane induced by the experimental procedure. However, there was no correlation between the severity of the blood pressure and the observed morphologic or functional disturbance in the glomerulus. It is concluded that the experimentally induced hypertension, like its human counterpart (essential hypertension), is not a consequence of renal ischemia nor is it dependent upon the concomitant presence of renal excretory insufficiency.

KAYDEN

METABOLIC EFFECTS ON CIRCULATION

Ballard, R. B., Danforth, W. H., Naegle, S., and Bing, R. J.: Myocardial Metabolism of Fatty Acids. J. Clin. Invest. **39**: 717 (May), 1960.

The myocardial extraction and usage of total and free fatty acids were determined in patients and dogs. In the fasting human subject the mean myocardial extraction of free fatty acids accounted for 42 per cent of the total fatty acid extraction while the esterified fraction made up the other 58 per cent. In the fasting dog, the free fatty acid fraction accounted for only 23 per cent of the total fatty acids extracted. The determination of the iodine numbers in the plasma revealed that there was proportionally a greater usage of the saturated than of the unsaturated fatty acids by the heart. The injection of a fat meal increased both plasma concentration and myocardial extraction of free fatty acids. A fall in the plasma concentration of total fatty acids and an increase in the concentration of free fatty acids occurred upon the administration of heparin. The authors concluded that the myocardial extraction of free fatty acids is usually dependent upon their arterial concentrations and that esterified fatty acids account for more than 50 per cent of the total fats extracted by the myocardium.

KARPMAN

Beznak, M.: The Role of Anterior Pituitary Hormones in Controlling Sizes, Work and Strength of the Heart. J. Physiol. **150**: 251 (Feb.), 1960.

The cardiac output and work, strength of the heart, heart rate, blood pressure, total peripheral resistance, oxygen consumption, respiration, blood volume, hematocrit, red cell count, and heart size were measured in hypophysectomized rats before and after treatment with a sheep pituitary powder and with 5 fractions prepared from it. Hypophysectomy produced hemodynamic changes such as bradycardia, hypotension, decreased cardiac output and work; these changes were found to be secondary to decreased metabolism and were prevented by administration of thyroid stimulating hormone (TSH). Aortic constriction produced cardiac hypertrophy only in

those hypophysectomized rats who had previously received treatment with a fraction containing growth hormone. The hypertrophy was greater in those groups receiving TSH as well as growth hormone, but TSH alone had very little effect. The author concluded that TSH prevented cardiac atrophy because of its metabolic effect, whereas cardiac hypertrophy was controlled by growth hormone. It was also noted that there was no interrelationship between the size of the heart and the work produced; the size of the heart was influenced by growth hormone, whereas the strength was controlled, in part, by TSH. All of the effects of the preparations used were explained by the relative contents of TSH, growth hormone and, to a lesser extent, an active adrenal component.

KARPMAN

Kien, G. A., Gomoll, A. W., Sherod, T. F.: Action of Digoxin and Insulin on Transport of Glucose through Myocardial Cell Membrane. Proc. Soc. Exper. Biol. & Med. **103**: 682 (Apr.), 1960.

The authors made a comparison of the effects of digoxin and insulin on the rate of transport of galactose into the myocardium of the intact anesthetized dog. Myocardial intracellular transportation of glucose was determined by measuring the rate of galactose-1-C^{14} entry and accumulation in the hearts of normal dogs. Three groups of 6 dogs were used. The first group received digoxin (0.065 mg./Kg.), the second group received insulin (1 unit/Kg.), and the third group served as a control. One half hour after drug administration, galactose-C^{14} was given (0.5μC/Kg.). The hearts were removed at 1-, 5- and 10-minute intervals, respectively, after administration of the isotope. The following results were noted: Administration of insulin or digoxin increased the extent to which galactose accumulated in the myocardium by 125 and 90 per cent respectively. At the 1-minute interval there was no significant difference in the arterial concentration of galactose-C^{14} in the 3 groups, but at the 5- and 10-minute intervals there was significantly less galactose in the blood of the treated groups than in the control group. There was no significant difference between the digoxin or the insulin group at any time. The administration of insulin and digoxin resulted in an increase in galactose entry and accumulation in the myocardium indicating an increase in the rate of glucose deposited in this tissue. The data support the conclusion that digoxin increases myocardial glucose metabolism by facilitating entry of the glucose into the myocardial cell.

KRAUSE

PATHOLOGY

Gillman, T., Grant, R. A., and Hathorn, M.: Histochemical and Chemical Studies of Calciferol-induced Vascular Injuries. Brit. J. Exper. Path. **41**: 1 (Feb.), 1960.

Calciferol was administered orally for 5 consecutive days to Wistar strain rats. Control rats were fed a daily quantity of food equal to that consumed by the calciferol-treated rats. The object of this study was to determine the histologic, histochemical, and chemical changes induced in the rat aorta by toxic doses of calciferol and to compare these with changes found in the heart muscle and coronary arteries. There was an exceptional deposition of calcium and phosphorus in the aorta, which deposition was unrelated to the serum calcium level and persisted in contrast to the disappearance of mineralization of the heart and coronary arteries. There was a prolonged rise in the serum mucoprotein level. Chemically, there was a rise in total aortic hexose and hexosamine to approximately double the control levels. The total aortic collagen appeared to increase toward the end of the experimental period, coinciding with the histologic appearance of aortic and coronary sclerosis. This supports the concept that healing in vascular wounds pursues a slower course than cutaneous wound healing.

KALMANSOHN

Szakacs, J. E., and Mehlman, B.: Pathologic Changes Induced by l-Norepinephrine. Quantitative Aspects Am. J. Cardiol. **5**: 619 (May, 1960.

Myocardial lesions consisting of focal necrosis or damage, inflammatory exudate, and hemorrhage have been observed in patients who received prolonged infusions of norepinephrine. In order to quantitate this apparent toxic effect of the drug, it was administered intravenously in various quantities to 28 dogs; and at an unspecified interval thereafter, the hearts were examined pathologically. Norepinephrine infusion at rates of 0.5 to 1.0 mcg. per Kg. per minute for periods up to 6 hours caused no appreciable cardiac damage. However, nearly all of the 20 animals receiving higher drug concentrations for 10 hours or less presented myocardial lesions which in 14 were gross and in 19 were microscopic. All of the myocarditis group had tachycardia and arrhythmia. The dogs infused with the highest concentrations of norepinephrine, 5 to 10 mcg. per Kg. per minute, died within ½ to 6 hours of cardiac arrest, cerebral hemorrhage, or pulmonary edema. The authors suggest that the therapeutic response to norepinephrine cannot be safely gaged by blood pressure change alone and

that a dose of 0.2 mcg. per Kg. per minute may approximate the safe limit for prolonged administration in man.

ROGERS

Uhley, H. N., and Rivkin, L.: Peripheral Distribution of the Canine A-V Conduction System. Am. J. Cardiol. 5: 688 (May), 1960.

Application of Lugol's solution to the endocardial surfaces of the canine heart has been found to stain the conduction system dark bluish-brown, due apparently to the rich glycogen content of the Purkinje tissue. After such staining, the gross structure of the system was studied in the hearts of 30 dogs. The left bundle of His appeared as a short, broad band on the left side of the ventricular septum, and it separated into anterior and posterior primary branches to the respective papillary muscles and into a rich network supplying the remaining septum and free wall musculature. The right bundle appeared on the right side of the septum as a long, narrow band extending to the anterior papillary muscle where it branched extensively. It was suggested that the structural differences between the right and left bundles may be related to the greater frequency of the right bundle-branch block noted clinically. A greater concentration of conduction tissue was noted in the areas of the ventricular septum that are activated early, whereas the upper portions of the septal surfaces are activated late, and were relatively free of Purkinje fibers.

ROGERS

PHARMACOLOGY

Arora, R. B., Sharma, P. L., Gupta, V, N., Lal, A., and Mathur, C N.: A Study on Mechanism of Cardiac Arrhythmias. Veratrine Response and Antiveratrine Action as a Common Property of Antiarrhythmic Drugs. Arch. int. Pharmacodyn. 123: 386 (Mar.), 1960.

Experiments were conducted to elucidate the basic mechanism of correlation of antiveratrinic and antiarrhythmic activity, observed to be a common property of 42 compounds reported so far. It has been proved quantitatively that the development of veratrine response by veratridine is associated with an efflux of potassium. Potassium per se in a concentration of 1:3000 was found to antagonize the development of veratrine response. Further, by increasing the potassium concentration of the bath fluid to one and one-half times the normal, it was possible to elicit the antiveratrinic action of antimalarial drugs studied as a group in lower concentrations. This concentration of potassium per se did not possess any antiveratrine action. Since the increase in potassium concentration of coronary sinus blood was found to be largely nonspecific in nature the correlation of antiveratrine and antiarrhythmic actions of drugs on the basis of atrial arrhythmias cannot be explained by the action of these drugs on efflux of potassium from the skeletal and cardiac muscle. There is no correlation between the antiarrhythmic and antiveratrine action of drugs on the basis of ventricular arrhythmias alone. The probable mechanisms responsible for this discrepancy are discussed.

BRACHFELD

Balagot, R. C., Reyes, R. M., and Sadove, M. S.: Efficacy of Silicone Antifoam Agents in the Control of Pulmonary Edema. Current Researches in Anesth. & Analg. 39: 197 (Mar.-Apr.), 1960.

Sixteen rabbits were brought for 30 minutes into an atmosphere of the nebulized test substance, injected intravenously with 2 mg. of epinephrine 1:1000, and then kept in this atmosphere until they died or were killed after 1 hour. Tested by their effect on survival time and the ratio of lung weight to body weight, a compound containing 0.005 per cent silicone DC antifoam AF in Alevaire was significantly more effective in the control of pulmonary edema than Aleivaire alone, and a compound containing 0.01 per cent antifoam was even more effective. Alevaire alone was slightly more effective than 2-ethyl hexanol.

LEPESCHKIN

Burn, J. H., and Hukovic, S.: Anoxia and Ventricular Fibrillation; with a Summary of Evidence on the Cause of Fibrillation. Brit. J. Pharmacol. 15: 67 (Mar.), 1960.

In the isolated, perfused, rabbit heart, electrically induced ventricular fibrillation usually was more persistent when the perfusate was saturated with a gas mixture containing a lower oxygen content (47.5 per cent vs. 95 per cent). This effect was attributed to a shortening of the duration of cardiac action potential caused by hypoxia. It was noted that several other factors that shorten the action potential—acetylcholine, dinitrophenol, calcium excess, glucose deficiency, potassium lack or marked excess—all may promote fibrillation. It appeared that the maintenance of a lengthy action potential prevented undue spread of excitation waves through the myocardium and therefore tended to prevent fibrillation.

ROGERS

NEWS FROM
THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York

Telephone Gramercy 7-9170

Association Awards $2 Million To Support 179 Investigators

Research awards totaling more than $2,000,000 to support 179 investigatorships and fellowships during the fiscal year beginning July 1, 1961, have been announced by the American Heart Association.

An additional group of national awards in the Grant-in-Aid category will be announced soon. They will bring to nearly $4,000,000 the sums allocated for research in fiscal 1961-62 by the Association's National Office. Together with research disbursements by affiliates and chapters, the Association's research support for the period will total approximately $10,000,000, largest in its history.

Included in the new allocations are sums for nine Career Investigators, 103 new and continued Established Investigators, 32 new and continued Advanced Research Fellows and 35 new and continued Research Fellows. Also included are supplementary grants to 22 Established Investigators to help underwrite the costs of technical assistance, equipment and supplies.

A complete list of recipients of the present awards appears at the end of this section.

May 15 is Abstracts Deadline For AHA Scientific Sessions

Abstracts of papers to be presented at the annual Scientific Sessions of the American Heart Association in Bal Harbour, Florida, October 20-22, 1961, must be submitted by May 15. Official application forms may be obtained from Richard E. Hurley, M.D., Medical Associate, American Heart Association, 44 East 23rd Street, New York 10, New York.

Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less and include a brief digest of the results obtained and conclusions reached.

Applications for space for *scientific exhibits,* which must be returned postmarked not later than May 15, 1961, may also be obtained from Dr. Hurley. Space for *industrial exhibits* may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, New York.

Arteriosclerosis Council Meeting; Abstracts of Papers Due May 15

The Annual Meeting of the AHA's Council on Arteriosclerosis will be held on October 18-20, 1961, immediately preceding the Association's annual Scientific Sessions at Bal Harbour, Florida.

The deadline for submitting abstracts of papers for presentation at the Council sessions is May 15. Abstracts must be limited to 250 words. Official application forms may be obtained from Jeremiah Stamler, M.D., Chicago Board of Health, 54 West Hubbard Street, Chicago 10, Illinois, or from the American Heart Association, 44 East 23rd Street, New York 10, New York.

Council sessions will be open to all interested individuals whether or not they are Council members. Also, abstracts of papers for presentation are invited from members and non-members.

World Cardiology Congress Scheduled For October 1962, in Mexico City

The Fourth World Congress of Cardiology will be held in Mexico City from October 7-13, 1962, Dr. I. Costero, Secretary General of the Organizing Committee, has announced.

Also serving on the committee to organize the Congress are Dr. I. Chavez, President, and Dr. R. Carral, Treasurer. Information concerning the sessions may be obtained from Dr. Costero, Ave. Cuauhtemoc, 300, Mexico, D. F.

Meetings Calendar

May 2-3: Association of American Physicians, Atlantic City. Paul Beeson, Yale University School of Medicine, New Haven 11, Connecticut.

May 5-7: American Society of Internal Medicine, Miami Beach. G. T. Bates, 350 Post St., San Francisco 8, California.

May 7-11: International College of Surgeons, North American Federation, Annual Congress, Chicago. H. E. Turner, 1516 Lake Shore Dr., Chicago 11, Illinois.

May 8-12: American College of Physicians, Miami Beach. E. C. Rosenow, Jr., 4200 Pine St., Philadelphia 4, Pennsylvania.

May 16-20: American College of Cardiology, New York. Philip Reichert, 350 Fifth Ave., New York 1, New York.

May 31-June 2: Canadian Federation of Biological Societies, Guelph, Ontario. E. H. Bensley, 1650 Cedar Ave., Montreal 25, Canada.

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois.

June 23-25: American College of Angiology, New York. Alfred Halpern, 11 Hampton Court, Great Neck, New York.

June 25: Society for Vascular Surgery, New York. George H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Maryland.

June 25-30: American Medical Association, Annual Meeting, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

July 1-4: International College of Surgeons, New England Regional Meeting, Chatham, Massachusetts. M. L. Brodny, 4646 N. Marine Dr., Chicago 40, Illinois.

August 7-10: National Medical Association, New York. John T. Givens, 1108 Church St., Norfolk, Virginia.

August 27-September 1: American Congress of Physical Medicine and Rehabilitation, Cleveland. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Illinois.

September 26-29: American Roentgen Ray Society, Miami Beach. C. A. Good, Mayo Clinic, Rochester, Minnesota.

October 2-6: American College of Surgeons, Chicago. W. E. Adams, 40 East Erie St., Chicago 11, Illinois.

October 20-24: American Heart Association, Annual Meeting and Scientific Sessions (October 20-22), Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.

November 13-17: American Public Health Association, Detroit. Berwin F. Mattison, 1790 Broadway, New York, 19, New York.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

November 27-30: American Medical Association, Clinical Meeting, Denver. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

Abroad

June 2-5: Latin-American Congress of Physical Medicine, Lisbon. C. L. deVictoria, 245 E. 17th St., New York, New York.

June 3-15: International Medical-Surgical Meetings, Turin, Italy. Minerva Medica, Corao Bramante 85, Turin.

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

September 3-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-9: International Congress of Angiology, Prague. Prof. Z. Reinis, IVth Medical Clinic, Praha 2/499, Czechoslovakia.

September 6-12: International Congress of Human Genetics, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 7-9: International Cardiovascular Society Congress, Dublin. H. Haimovici, 715 Park Ave., New York 21, New York.

September 10-15: International Neurological Congress, Rome. G. Alema, Vialo Universita, 30 Rome, Italy.

1962

October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico, D.F.

AHA Award Recipients

Following is a list of investigators who will be supported by the American Heart Association during the fiscal year beginning July 1, 1961:

Career Investigators

Coons, Albert H. Harvard Medical School, Boston.

Lorber, Victor, University of Minnesota Medical School, Minneapolis.

Morales, Manuel F. University of California Medical Center, San Francisco.

Pappenheimer, John R. Harvard Medical School, Boston.

Ratnoff, Oscar D. Western Reserve University School of Medicine, Cleveland.

Sprinson, David B. Columbia University College of Physicians and Surgeons, New York.

Taggart, John V. Columbia University College of Physicians and Surgeons, New York.

Wannamaker, Lewis W. University of Minnesota School of Medicine, Minneapolis.

Zilversmit, Donald B. University of Tennessee College of Medicine, Memphis.

Continued Established Investigators

Albrink, Margaret J. Effect of metabolic and nutritional factors on serum lipids. Yale University School of Medicine, New Haven.

Benesch, Reinhold. Role of sulfhydryl and disulfide groups in biological systems. Columbia University College of Physicians and Surgeons, New York.

Bloomfield, Daniel K. Comparative enzymology of the conversion of cholesterol to bile acid. Western Reserve University School of Medicine, Cleveland.

Bricker, Neal S. Pathological physiology of chronic Bright's disease. Washington University School of Medicine, St. Louis.

Briggs, F. Norman. Muscle relaxation—biochemical studies. Tufts University School of Medicine, Boston.

Combes, Burton. Hepatic metabolism during hepatoportal hemodynamic adjustments. University of Texas Southwestern Medical School, Dallas.

Cooper, David Y. Steroid formation in essential hypertension. University of Pennsylvania School of Medicine, Philadelphia.

Corcoran, John W. Metabolism of the branched chain monosaccharides and their role in the mammalian and bacterial cell. Western Reserve University School of Medicine, Cleveland.

Daly, Marie M. Arterial metabolism in hypertension. Albert Einstein College of Medicine of Yeshiva University, New York.

DeWall, Richard A. Perfusion techniques as applied to open cardiac surgery. University of Minnesota Medical School, Minneapolis.

Dickerman, Herbert W. Basic amino acid transport and metabolism in the kidney. Johns Hopkins University School of Medicine, Baltimore.

DuBois, Arthur B. Gas exchange in the lungs, mechanics of breathing and pulmonary capillary blood flow. University of Pennsylvania Graduate School of Medicine, Philadelphia.

Eckstein, John W. Venomotor responses to circulatory alterations in man. State University of Iowa College of Medicine, Iowa City.

Elwyn, David H. Quantitative aspects of amino acid metabolism. Michael Reese Hospital and Medical Center, Chicago.

Farrell, Gordon L. Physiological factors which regulate the secretion of aldosterone. Western Reserve University School of Medicine, Cleveland.

Feinberg, Harold. Myocardial metabolism and cardiac dynamics. Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago.

Fresco, Jacques R. Macromolecular aspects of nucleic acid structure and function. Princeton University, Princeton, New Jersey.

Gamble, James L., Jr. Mitochondrial function in relation to electrolyte transport. Johns Hopkins University School of Medicine, Baltimore.

Gentsch, Thomas O. (I) Remote stimulation by radio frequency transmission. (II) Development of a vertical membrane oxygenator and the effects of extra-corporeal bypass on the heart. Yale University School of Medicine, New Haven.

Gibson, David M. Enzymatic synthesis of fatty acids in animal tissues. Indiana University School of Medicine, Indianapolis.

Gidez, Lewis I. Factors determining serum lipid composition and concentration. Albert Einstein College of Medicine of Yeshiva University, New York.

Giebisch, Gerhard. Ion transport across renal tubules of the amphibian and mammalian kidney, utilizing micropuncture techniques. Cornell University Medical College, New York.

Gilbert, James B. Role and site of binding of the metal ion in metal-containing or metal-activated enzymes. Clayton Foundation Biochemical Institute, University of Texas, Austin.

Gitlin, David. Blood and tissue proteins. Harvard Medical School, Boston.

Goldthwait, David A. Biosynthesis of purine nucleotides and of ribonucleic acid. Western Reserve University School of Medicine, Cleveland.

Gottschalk, Carl W. Micropuncture study of kidney function. University of North Carolina School of Medicine, Chapel Hill.

Hanenson, Irwin B. Relationship of the kidney, liver and adrenal glands to arterial hypertension. May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Hatch, Frederick T. Biosynthesis and degradation of lipoproteins. Massachusetts General Hospital, Boston.

Henly, Walter S. Determination of myocardial blood flow in the intact subject, utilizing radioiodinated (I^{131}) human serum albumin. Baylor University College of Medicine, Houston.

Hougie, Cecil. Blood clotting and fibrinolytic enzyme systems. University of Washington School of Medicine, Seattle.

Huckabee, William E. Metabolic reactions to circulatory disturbances and their role in the control

of the circulation. Massachusetts Memorial Hospitals, Boston.

Jacobs, Earl E. Structural factors involved in mitochondrial oxidative phosphorylation mechanisms. Stanford University, Stanford, California.

Kaplan, Melvin H. Localization of tissue-deposited streptococcal antigens and antibodies in animal and human tissues by means of the fluorescein-labeling technique; pathogenesis of rheumatic fever and rheumatic heart disease in relationship to the autoimmune theory of pathogenesis. Cleveland Metropolitan General Hospital.

Katz, Yale J. Renal revascularization in experimental hypertension and renal insufficiency. University of Southern California School of Medicine, Los Angeles.

Khairallah, Philip A. Reactivity of blood vessels. Cleveland Clinic.

Lewis, David H. Regulation of the circulation in man. Philadelphia General Hospital.

Maley, Gladys F. Interconversions of nucleotides in embryonic and neoplastic tissues. New York State Department of Health, Albany.

Mann, George V. Cause and prevention of atherosclerosis. Vanderbilt University School of Medicine, Nashville.

Markus, Gabor. Clinical and biochemical studies on the fibrinolytic system in man. Roswell Park Memorial Institute, Buffalo, New York.

Martin, Harry B. Collateral ventilation and alveolar rupture pressure. Harvard University School of Public Health, Boston.

Morgan, Richard S. Ribonucleic acid structures. Brandeis University, Waltham, Massachusetts.

Mueller, Helmut. Characterization of the relaxing factor and its interaction with contractile proteins. University of Pittsburgh Graduate School of Public Health.

Padawer, Jacques. Physiology of the mast cell and its relation to cardiovascular function and disease. Albert Einstein College of Medicine of Yeshiva University, New York.

Page, Ernest. Ion fluxes in mammalian heart muscle. Harvard Medical School, Boston.

Pick, Ruth. Pathogenesis of atherosclerosis and its sequelae. Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago.

Pollak, Victor E. Investigations on the kidney in health and disease. University of Illinois College of Medicine, Chicago.

Portman, Oscar W. Dietary factors affecting cholesterol catabolism and atherosclerosis. Harvard University School of Public Health, Boston.

Richmond, Jonas E. Role of the prosthetic group of proteins in the biosynthesis and metabolism of conjugated proteins. Harvard Medical School, Boston.

Rubin, Albert L. Investigation of the metabolic alterations in the uremic syndrome. Cornell University Medical College and New York Hospital, New York.

Rudolph, Abraham M. Pulmonary hypertension in congenital heart disease. Albert Einstein College of Medicine of Yeshiva University, New York.

Savitsky, J. Philip. Metabolic regulatory effects of desoxyribonucleic acids. Montefiore Hospital, New York.

Schmidt-Nielson, Bodil M. Comparative kidney physiology. Duke University, Durham, North Carolina.

Shumway, Norman E. Ventricular fibrillation by threshold determinations. Stanford University School of Medicine, Palo Alto, California.

Springer, Georg F. Plant polysaccharides in relation to lipemia clearing, coagulation, blood group specificity and infectious mononucleosis. Hospital of the University of Pennsylvania, Philadelphia.

Staple, Ezra. Metabolism of cholesterol, mechanisms of synthesis and breakdown of related substances. University of Pennsylvania School of Medicine, Philadelphia.

Straus, Werner. Investigation of "phagosomes" in various tissues of the rat. University of Louvain, Louvain, Belgium.

Szent-Gyorgyi, Andrew G. Structure of myosin. Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Massachusetts.

Travis, Randall H. Aldosterone in congestive heart failure. University Hospitals of Cleveland and Western Reserve University School of Medicine, Cleveland.

Tsuboi, Kenneth K. Metabolism of nucleotides and related compounds in cardiac tissues. Stanford University School of Medicine, Palo Alto, California.

Ulrich, Frank. Ion transport by subcellular particles. Yale University School of Medicine, New Haven.

Vernier, Robert L. Etiology and pathogenesis of diffuse cardiovascular disease in childhood. University of Minnesota Medical School, Minneapolis.

Warner, Homer R. Application of analogue computer techniques to the study of regulation of the circulation. University of Utah College of Medicine and Latter-day Saints Hospital, Salt Lake City, Utah.

Ziegler, Daniel M. Mitochondrial electron transport system. Institute for Enzyme Research, University of Wisconsin, Madison.

New Established Investigators

Craig, Albert B., Jr. Relationships of carbohydrate and potassium metabolism. University of Rochester School of Medicine and Dentistry, Rochester, New York.

Dennis, Warren H. Relationship between membrane structure and permeability. University of Louisville School of Medicine, Louisville, Kentucky.

Fales, John T. Oxygen consumption and heat pro-

duction of resting and working skeletal muscle. Johns Hopkins University School of Hygiene and Public Health, Baltimore.

Fasman, Gerald D. Synthesis and use of synthetic polyamino acids as models of proteins in structural and biological studies. Children's Cancer Research Foundation, Boston.

Fillios, Louis C. Purine and pyrimidine metabolism in experimental atherosclerosis. Harvard University School of Public Health, Boston.

Glauser, Stanley C. Molecular physiology of normal and abnormal hemoproteins. University of Pennsylvania Graduate School of Medicine, Philadelphia.

Lacy, William W. Metabolism in uremia. Vanderbilt University School of Medicine, Nashville, Tennessee.

Lowey, Susan. Chemistry of muscle proteins. Children's Cancer Research Foundation, Boston.

Martonosi, Anthony N. Functional groups of actin participating in the actin-actin, actin-ATP and actin-myosin interaction. Retina Foundation, Boston.

Nathan, Paul. Transplantation reaction in kidney and skin. May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Peifer, James J. Metabolism of lipids found in the blood-vascular system. Hormel Institute, University of Minnesota, Austin, Minnesota.

Samuels, Arthur J. Immuno-enzymology of heart muscle proteins; search for immuno-chemical evidence for configurational changes in enzymes of heart muscles during congestive failure. Dartmouth Medical School, Hanover, New Hampshire.

Sperelakis, Nick. Conduction in heart. Western Reserve University School of Medicine, Cleveland.

Stoffyn, Pierre J. Biochemistry of heparin and related substances. Massachusetts General Hospital, Boston.

Ways, Peter O. Membrane lipids in normal and pathological red blood cells of man. University of Washington School of Medicine, Seattle.

Wells, William W. Lactose diets and cholesterol metabolism. University of Pittsburgh School of Medicine.

Welsh, Richard S. Characterization of undegraded, non-fibrous forms of desoxyribonucleoprotein from calf thymus. University of Redlands, Redlands, California.

Wortman, Bernard. Mucopolysaccharides of the nervous system and its blood vessels, with particular reference to the retina. Washington University School of Medicine, St. Louis.

Continued Established Investigator-Grantees

Brady, Allan J. Link between excitation and contraction. University of California at Los Angeles Medical Center.

Clayton, Raymond B. Function and utilization of sterols in insects. Harvard University, Cambridge, Massachusetts.

Conway, F. James. Aging of arteries in relation to hypertension. University of Michigan Medical School, Ann Arbor.

Dallam, R. Duncan. Cellular chemistry and bioenergetics. University of Louisville School of Medicine, Louisville, Kentucky.

Despopoulos, Agamemnon. Parameters of cellular transport phenomena. University of Louisville School of Medicine, Louisville, Kentucky.

Durbin, Richard P. Transport of water and HCl by the stomach. Harvard Medical School, Boston.

Goldstein, Robert. Isolation and identification of prothrombin and "serum factors"; investigation of their role in coagulation and thrombosis. New England Center Hospital, Boston.

Gubler, Clark J. Enzymatic functions of thiamin. Brigham Young University, Provo, Utah.

Harris, John B. Interrelationships between bioelectrical properties and electrolyte transport. University of California School of Medicine, San Francisco.

Hefner, Lloyd L. Relationships between heat production, oxygen consumption and work of the mammalian heart. Medical College of Alabama, Birmingham.

Hirschhorn, Kurt. Genetic and metabolic aspects of atherosclerosis. New York University Post-Graduate Medical School, New York.

Landau, Bernard R. Carbohydrate metabolism in hyperthyroidism. Western Reserve University School of Medicine, Cleveland.

Watanabe, Shizuo. Mechanism of relaxation of glycerol-treated muscle fibers. University of California Medical Center, San Francisco.

Wilson, Jean D. Mechanism of neutral sterol secretion into the gut. University of Texas Southwestern Medical School, Dallas.

New Established Investigator-Grantees

Goodkind, M. Jay. Endocrine effects on myocardial metabolism and ventricular function. Yale University School of Medicine, New Haven.

Katz, Joseph. Intermediate metabolism of lactating mammary gland. Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.

LaBella, Frank S. Anterior and posterior pituitary hormones; formation, secretion and action on connective tissue. University of Manitoba Faculty of Medicine, Winnipeg, Canada.

Levitin, Howard. Concentrating and diluting functions of the kidney. Yale University School of Medicine, New Haven.

Maffly, Roy H. Coupling of metabolic energy and active sodium transport. University of California School of Medicine, San Francisco.

Regan, Timothy J. Metabolic basis of ion transport

in the heart and relationship to its functional properties. Seton Hall College of Medicine and Dentistry, Jersey City, New Jersey.

Soroff, Harry S. (I) Metabolic and hemodynamic effects of assisted circulation; (II) Development of partial and complete prostheses for replacement of diseased aortic and mitral valves. New England Center Hospital, Boston.

Spiro, Robert G. Structure and metabolism of glycoproteins. Harvard Medical School at Baker Clinic Research Laboratory, Boston.

Continued Advanced Research Fellows

Abboud, Francois M. Vascular hypertensitivity to norepinephrine in man. Under John W. Eckstein, State University of Iowa College of Medicine, Iowa City.

Adamis, Dionysios. Development of thrombolytic and anticoagulating agents from molds and plants. Under Mario Stefanini, Saint Elizabeth's Hospital, Boston.

Bowman, Roger H. Normal and fasting metabolism of cardiac muscle and the hormonal influences involved. Under F. G. Young, University of Cambridge, Cambridge, England.

Carrasquer, Gaspar. Electrolyte and water function of the kidney; mechanism of tubular ion transport and acidification of the urine. Under William A. Brodsky, University of Louisville School of Medicine, Louisville, Kentucky.

Cohen, Louis. Phospholipid composition of serum lipoproteins and the coagulant activity of serum phospholipids in health and coronary artery disease. Under Richard J. Jones, University of Chicago School of Medicine.

Cummings, Nancy B. Alterations in metabolism in renal disease. Under DeWitt Stetten, Jr., National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland.

Ellis, H. Alan. Effects of quinidine on carbohydrate metabolism. Under Robert H. Furman, Oklahoma Medical Research Foundation, Oklahoma City.

Glagov, Seymour. Distribution of atherosclerosis in the major arteries as a function of altered circulatory conditions in the supplied organs. Under Donald A. Rowley, University of Chicago School of Medicine.

Hall, Philip W., III. Water and electrolyte balances in patients with refractory edema. Under George J. Gabuzda, Cleveland Metropolitan General Hospital.

Hays, Richard M. Mechanism of action of antidiuretic hormone. Under Irving M. London, Albert Einstein College of Medicine of Yeshiva University, New York.

Hess, Marilyn E. Influence of hormones on the enzymatic and functional activity of heart muscle. Under Niels Haugaard, University of Pennsylvania School of Medicine, Philadelphia.

Jensen, David. Basic mechanisms of cardiac automatism. Under Per F. Scholander, University of California, Scripps Institution of Oceanography, La Jolla, California.

Lauler, David P. (I) Nephron population in acute renal failure; (II) Blood-cerebrospinal fluid barrier in uremia; (III) Effect of low salt diet on renal function in chronic renal disease. Under John P. Merrill, Peter Bent Brigham Hospital, Boston.

Miller, Tracy B. Hyaluronidase and the action of the antidiuretic hormone. Under Alfred E. Farah, State University of New York Upstate Medical Center, Syracuse.

Radding, Charles M. Biochemical basis of genetics. Under Arthur Kornberg, Stanford University School of Medicine, Palo Alto, California.

Ronwin, Edward. Enzymes involved in blood clotting and fibrinolysis; biochemical characterization of the processes. Under George P. Hager, University of Minnesota College of Pharmacy, Minneapolis.

Shabetai, Ralph. Effects of pharmacologic agents on the pulmonary circulation. Under Noble O. Fowler, Cincinnati General Hospital.

Shneour, Elie A. Biosynthesis of carotenoids in nonsulfur purple bacteria. Under Melvin Calvin, University of California, Berkeley.

Wexler, Bernard C. Pathology and endocrinology of arteriosclerosis in the rat. Under Benjamin F. Miller, May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Yaffe, Sumner J. Metabolic basis for the renal concentrating mechanism. Under Norman Kretchmer, Stanford University School of Medicine, Palo Alto, California.

New Advanced Research Fellows

Barnett, Lewis B. Mechanism of enzyme adaptation. Under J. Th. G. Overbeek, State University of Utrecht, Utrecht, The Netherlands.

Blair, Emil. Physiological, morphological and surgical study of experimental coronary thrombosis and myocardial infarction. Under R. Adams Cowley, University of Maryland School of Medicine, Baltimore.

Herd, J. Alan. Role of the autonomic nervous system in coronary heart disease. Under A. Clifford Barger, Harvard Medical School, Boston.

Humphries, J. O'Neal. Correlation of the intracardiac and external phonocardiogram with other measures of hemodynamic events in humans and in the laboratory animal. Under Victor A. McKusick and Richard S. Ross, Johns Hopkins University School of Medicine, Baltimore.

Jackson, Benjamin T. Fetal cardiovascular physiology, normal and pathological. Under Richard H. Egdahl, Medical College of Virginia, Richmond.

Katz, Arnold M. Alterations of structural proteins

of the myocardium in heart failure. Under Wilfried F. H. M. Mommaerts, University of California at Los Angeles Medical Center.

Kittinger, George W. Biochemical approaches to experimentally induced arteriosclerosis in rats. Under Benjamin F. Miller, May Institute for Medical Research of the Jewish Hospital Association, Cincinnati.

Knowlan, Donald M. Effect of uremia upon cardiac metabolism. Under Robert E. Olson, University of Pittsburgh Graduate School of Public Health.

Lubash, Glenn D. Biochemical abnormalities in patients with renal disease. Under Albert L. Rubin, Second (Cornell) Medical Division, Bellevue Hospital, New York.

Manning, John W. Central integration of cardiovascular activity. Under Marion deV. Cotten, Emory University School of Medicine, Atlanta.

Monroe, Robert G. Physical and pharmacological factors affecting myocardial metabolism. Under Alexander S. Nadas, Children's Hospital Medical Center, Boston.

Weissmann, Gerald. Experimental alteration of connective tissue cells in culture. Under Lewis Thomas, New York University School of Medicine, New York.

Continued Research Fellows

Criley, John Michael. (I) Exaggerated natriuresis in congenital heart disease. (II) Clinical-physiological correlations in cardiovascular disease. Under E. Cowles Andrus and Richard S. Ross, Johns Hopkins Hospital, Baltimore.

Grant, C. Mackenzie. (I) Method for the quantitative study of pulmonary congestion and edema; (II) Function of the atria in man. Under David G. Greene, University of Buffalo School of Medicine and Buffalo General Hospital, Buffalo, New York.

Lancestremere, Ruben G. Relationship of renal function to cardiac output in patients with Laennec's cirrhosis. Under Solomon Papper, Medical College of Virginia, Richmond.

Mahadevan, Vaidyanath. Lipids in relation to blood coagulation. Under Walter O. Lundberg, Hormel Institute, University of Minnesota, Austin, Minnesota.

Manis, James. Active transport of calcium by the small intestine and the effect of vitamin D. Under David Schachter, Columbia University College of Physicians and Surgeons, New York.

Rainey, Robert L. Renal hemodynamics in abnormal cardiac function. Under James W. Culbertson, University of Tennessee College of Medicine, Memphis.

Vagnucci, Antonio I. Diurnal cycle of renal glomerular filtration and blood flow as correlated with electrolyte excretion in normal and hypertensive subjects. Under Laurence G. Wesson, New York University Post-Graduate Medical School, New York.

New Research Fellows

Botticelli, James T. Hemodynamics and electrolyte changes (extracellular-intracellular) following extracorporeal hemodialysis and digitalization. Under John H. Huston, Marquette University School of Medicine and Milwaukee County General Hospital, Milwaukee.

Charlier, Andre A. Measurement of stroke volumes in dogs by electromagnetic flowmeter and by dye-dilution technique. Under Julius H. Comroe, Jr., University of California Medical Center, San Francisco.

Conrad, Margaret C. Pathophysiology of peripheral vascular diseases. Under Harold D. Green, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.

Constantinos, Ingeborg. Changes in blood chemistry during disease. Under Baldew R. Bhussry, Georgetown University School of Medicine, Washington, D.C.

Dempsey, Mary E. Enzymatic conversions of cholesterol biosynthesis. Under Ivan D. Frantz, Jr., University of Minnesota Medical School, Minneapolis.

Duke, Martin. Circulation in anemia. Under Walter H. Abelmann, Boston City Hospital.

Guillory, Richard J. Biochemical studies related to problems regarding the control of cellular metabolism. Under E. C. Slater, University of Amsterdam, Amsterdam, The Netherlands.

Gulotta, Stephen J. Distribution and metabolism of digitalis steroids in man. Under Daniel S. Lukas, Cornell University Medical College, New York.

Heider, Charles H. Hemodialysis for chronic renal failure. Under Albert N. Brest and John H. Moyer, Hahnemann Medical College and Hospital, Philadelphia.

Hoak, John C. Significant factors in the production and inhibition of thrombosis. Under William E. Connor and Emory D. Warner, State University of Iowa College of Medicine, Iowa City.

Kazemi, Homayoun. Effect of acidosis on cardiac frequency. Under John C. Mithoefer, Mary Imogene Bassett Hospital, Cooperstown, New York.

Kopald, Hugh H. Mechanisms of sodium retention in experimental congestive heart failure. Under A. Clifford Barger, Harvard Medical School, Boston.

Landry, Arthur B., Jr. Lactate pyruvate metabolism in relation to parameters of cardiac function during standing exercise. Under Allen V. N. Goodyer, Grace-New Haven Hospital, New Haven, Connecticut.

Matloff, Jack M. Surgical studies of heart-lung grafts. Under Ralph A. Deterling, Jr., New England Center Hospital, Boston.

Niesenbaum, Leonard. Instantaneous pulmonary vascular resistance. Under Harry Goldberg, Albert Einstein Medical Center, Philadelphia.

Paiewonsky, Donald. Coronary circulation and cardiac metabolism under normal and pathological conditions. Under Rene Wegria, Saint Louis University School of Medicine, St. Louis.

Piemme, Thomas E. Mitral regurgitation; pulmonary circulation dynamics. Under Lewis Dexter, Peter Bent Brigham Hospital, Boston.

Rolett, Ellis L. Coronary circulation in health and disease. Under Richard Gorlin, Peter Bent Brigham Hospital, Boston.

Rowshan, Ghodratolah. Newborn circulation by serial dye-dilution curves. Under Herbert S. Harned, Jr., University of North Carolina School of Medicine, Chapel Hill.

Russell, Attie Y. H. Effects of coronary blood flow on the electrocardiographic changes associated with ventricular overwork in aortic stenosis and pulmonic stenosis. Under Abraham M. Rudolph, Albert Einstein College of Medicine of Yeshiva University, New York.

Scherr, Edward S. Respiratory gas exchange in pulmonary venous congestion and pulmonary edema. Under Frank D. Gray, Jr., Yale University School of Medicine, New Haven.

Strauss, Carl, F., Jr. Hepatic circulation and function in sickle cell anemia. Under James W. Culbertson, University of Tennessee College of Medicine, Memphis,

Sumner, Robert G. Anatomic and clinical studies on cardiac hypertrophy in systolic and diastolic overloading in dogs. Under Henry D. McIntosh, Duke Hospital, Durham, North Carolina.

Tabet, Robert C. Correlation of the circulatory response to tilting with the degree of arterial rigidity. Under John H. Huston, Marquette University School of Medicine and Milwaukee County Hospital, Milwaukee.

Taylor, Anna N. Definition of areas in the brain stem, primarily in midbrain and epithalamus, concerned with electrolyte metabolism and the control of aldosterone secretion. Under Gordon L. Farrell, Western Reserve University School of Medicine, Cleveland.

Temple, William E. Pulmonary arterial and venous gas and acid-base relationships to pressure and resistance. Under Peter V. Moulder, University of Chicago Clinics, Chicago.

Vaughan-Potter, Elizabeth. Artificially induced and naturally acquired immunity to group A streptococci. Under Gene H. Stollerman, Northwestern University Medical School, Chicago.

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